Title: Prospective Observational Study to Evaluate Medication-taking Behavior With Denosumab (Prolia®) and Patient Characteristics in Postmenopausal Women With Osteoporosis in Routine Clinical Practice in Germany, Austria, Greece and Belgium

AMG 162 - Prolia® (Denosumab)

Amgen Protocol Number 20110126

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Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled Prospective Observational Study to Evaluate Medication-taking Behavior With Denosumab (Prolia®) and Patient Characteristics in Postmenopausal Women With Osteoporosis in Routine Clinical Practice in Germany, Austria, Greece and Belgium, dated **14 December 2012**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

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 Principal Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: Prospective Observational Study to Evaluate Medication-taking Behavior With Denosumab (Prolia®) and Patient Characteristics in Postmenopausal Women With Osteoporosis in Routine Clinical Practice in Germany, Austria, Greece and Belgium

Study Phase: Observational

Indication: Treatment of osteoporosis (OP) in postmenopausal women at increased risk of fractures.

Study Objective: The objective of this observational study is to describe medication-taking behavior of patients treated with denosumab (Prolia®) for postmenopausal osteoporosis (PMO) at 12 and 24 months, using different specific measures (including persistence, adherence and medication coverage ratio). In addition, the study will provide the ability to assess medication-taking behavior in pre-defined subgroups of interest. The study aims also to describe the profile of patients treated with Prolia® for PMO in Germany, Austria, Greece and Belgium.

Safety Objective: To monitor the safety of patients administered Prolia® in a non-interventional setting.

Hypotheses: The study is descriptive in nature, and a formal hypothesis will not be tested in this observational study. However, measures of medication-taking behavior (compassing persistence, adherence and medication coverage ratio) with Prolia® at 12 and 24 months will be estimated.

Study Outcome Measures: The medication-taking behavior endpoints are:

- Persistence (yes/no) with Prolia® at 12 months
- Persistence (yes/no) with Prolia® at 24 months
- Adherence (yes/no) with Prolia® at 12 months
- Adherence (yes/no) with Prolia® at 24 months
- Medication Coverage Ratio (MCR) at 12 months
- Medication Coverage Ratio (MCR) at 24 months

Other outcome measures are:

- Time to non-persistence over 24 months
- Number of Prolia® injections within the specified window over 24 months
- Safety: the incidence of adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs).

Study Design: This is a multi-center observational study in postmenopausal women with osteoporosis who receive Prolia® Q6M, SC according to the applicable approved Prescribing Information (eg EU Summary of Product Characteristics (SmPC) or equivalent) for the treatment of PMO in routine clinical practice. This study is non-interventional and will not alter the routine clinical management of patients. It will comply with all applicable local regulations on a country-by-country basis. Eligible patients at participating sites initiating Prolia® should be enrolled in a sequential manner. A log should be maintained of all patients receiving Prolia® but not enrolled, including the reason for not enrolling.

Approximately 1500 postmenopausal patients administered Q6M SC Prolia® (denosumab 60 mg) for osteoporosis (600 in Germany and 300 each in Austria, Greece and Belgium) will participate from about 170 representative (country specific) sites (60 in Germany and 30 each in Austria, Greece and 50 in Belgium).

Patients will be asked to complete two short patient profile and health related quality of life questionnaires at study enrollment on a voluntary basis: If permitted by local regulations, patients will be asked to complete two brief Patient Reported Outcome (PRO) questionnaires related to treatment adherence to medication (Morisky Medication Adherence Scale 8-Item (MMAS-8)) and health status (Short Form (SF-12) Generic Health-Related Quality of Life Instrument). All other information will be collected from patient records at the investigator sites.

Site selection will be done with the aim of representing PMO care in each country with regards to type and location of site.

Enrollment is expected to last approximately 12 months and the patients will be followed for a period of 2 years after study enrollment. Given the 6 monthly administration frequency of Prolia®, a 24-month observation period is thought to be adequate to reliably ascertain medication-taking behaviors (adherence) outcomes in routine clinical practice for this non-interventional study.

As per definition, apart from being asked to voluntarily complete two short questionnaires on enrollment day (baseline), this observational study will not alter the routine clinical management of patients. Patients enrolled into this study will not be required to perform any other additional assessments (laboratory or diagnostic) for the specific purposes of the study. The decision to treat with Prolia® must occur prior to and independently of study considerations and before enrollment into the study (maximum 4 weeks from first injection). However, the decision to treat with Prolia®, the first Prolia® injection, obtaining the appropriate written informed consent (as required per local country regulations) and enrollment to the study, can happen at the same visit to avoid extra patient visits and to avoid interfering with country-specific routine clinical practice. Patients are expected to return to the clinic approximately every 6 months as part of her routine clinical care.

All data recorded will be collected per routine clinical practice including non-serious and serious adverse drug reactions.

No laboratory or diagnostic assessment is performed in the study. The overall study design is described in a study schema at the end of the protocol synopsis section.

Sample Size: Approximately 1500 patients (600 in Germany and 300 each in Austria, Greece and Belgium).

Summary of Subject Eligibility Criteria: Patients will meet the following inclusion criteria at enrollment into the study:

- Indicated for treatment of OP in postmenopausal women at increased risk of fractures according to the approved Regional Prescribing Information (eg, EU SmPC in Germany, Austria, Greece and Belgium).
- Enrolled into the study within 4 weeks of receiving their first injection of denosumab (Prolia®) according to the approved Regional Prescribing Information (eg, EU SmPC in Germany, Austria, Greece and Belgium).
- Appropriate written informed consent has been obtained (as required per local country regulations).

Patients meeting any of the following exclusion criteria are not eligible for participation in the study:

- Patient is currently enrolled in or has been enrolled within the prior 6 months in a study involving any investigational procedure, device or drug.
- Contraindicated for treatment with Prolia® according to the approved Regional Prescribing Information (eg, EU SmPC in Germany, Austria, Greece and Belgium).
- Participation in ongoing or previous denosumab clinical trials.
- Patient has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the patient to give written informed consent.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration: None

Non Amgen Investigational Product Dosage and Administration: None

Procedures: This observational study will not have any required procedures, assessments or changes to routine management of patients. It is anticipated that patients will visit their physician/health care provider (HCP) approximately once every 6 months for their six monthly Prolia® injection as part of their routine clinical care. Patients will be observed for 2 years following their study enrollment. Each site needs to be able to continually follow up patients for 2 years, to ensure that required data, including date of injection, can be obtained. Patient data

will be requested for transcription to an anonymous (eCRF) by site personnel. Details of the data to be collected are listed in Section 7 and Appendix A (Schedule of Data Collection).

The covariates to be captured in the study are listed in Section 10.1.3.

Statistical Considerations: The analyses will be based on the full analysis set (FAS) defined as all enrolled patients satisfying the inclusion/exclusion criteria that receive at least one Prolia® injection and have a non-missing enrollment date. In general, data summaries will be presented overall and by country.

Categorical outcomes will be summarized by the number and percentage 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.

Baseline characteristics will be summarized using descriptive statistics. The baseline characteristics of the patients will be compared across countries to identify possible differences. Missing covariate information will be compared as well across countries to identify potential sources of heterogeneity.

For the categorical measures of medication-taking behavior (persistence and adherence), the number and percentage of patients satisfying each of the medication-taking behavior outcomes at 12 and 24 months will be summarized overall and by country, and the associated 95% confidence intervals will be presented. Similarly for the continuous medication coverage ratio (MCR) outcome at 12 and 24 months, mean estimates and the associated 95% confidence intervals will be presented.

Analysis by Covariates: Summary statistics for each medication-taking behavior outcome will be provided by country and each of the subgroups defined by the covariates of interest.

In addition, univariate logistic regression will be used to explore the association of each pre-specified covariate with selected medication-taking behavior (persistence and adherence) at 24 months. For each covariate entered individually in the model, point estimates of the odds ratio, and 95% confidence intervals will be provided.

Moreover, a multivariate logistic regression including selected covariates that showed possible association with selected medication-taking behavior from the univariate analyses at 24 months will also be performed to identify predictors of selected medication-taking behavior to Prolia® at 24 months. A stepwise model selection will be implemented using SAS LOGISTIC procedure.

Time to non-persistence will be summarized by Kaplan-Meier methodology at the end of the study.

The number of Prolia® injections administrated within the specified window over 24 months will be summarized.

An interim analysis is planned to describe patient characteristics and ascertain the persistent rate with Prolia® treatment at 12 months, overall and for pre-defined subgroups defined by covariates of interest. Since the persistent rate at 12 months only involves the first 2 Prolia® injections, the interim analysis will be conducted when all patients have had the opportunity to receive their second Prolia® injection within the allowable window for persistence (6 months plus 12 weeks from the initial Prolia® injection). Any data collected after this date will not be included in the interim analysis. This interim analysis is planned to proactively inform reimbursement authorities if needed. The design of the study will not change based on the interim analysis results. No stopping rules will be applied due to the observational nature of this study.

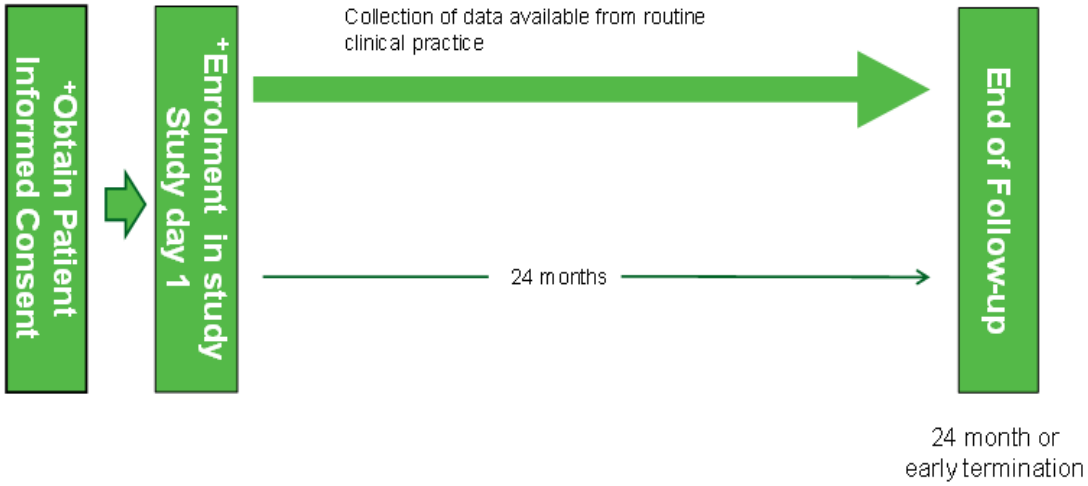
Safety: All serious and non-serious ADRs to Prolia® will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Patient incidence of serious and non-serious ADRs leading to discontinuation of Prolia® and serious ADRs associated with fatal outcome will be tabulated by system organ class and preferred term.

For a full description of statistical analysis methods, please refer to Section 10.4.2.

Sponsor: Amgen Inc.

Study Design and Treatment Schema

20110126: Prospective Observational Study to Evaluate Medication-taking Behavior With Denosumab (Prolia®) and Patient Characteristics in Postmenopausal Women With Osteoporosis in Routine Clinical Practice in Germany, Austria, Greece and Belgium



+The decision to treat with Prolia® 60 mg Q6M, the first denosumab injection, to obtain the appropriate written informed consent and enrolment in study can happen at the same visit to avoid extra subject visits and to avoid interfering with routine clinical practice. However, the decision to treat with Prolia® and the first injection of Prolia® must happen independently of study considerations. Enrolment in the study can occur within 4 weeks following the first Prolia® injection.

Subjects are expected to receive scheduled injection of Prolia® every 6 months as part of their routine clinical care

Study Glossary

Abbreviation or Term	Definition/Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
BMD	Bone Mineral Density
BPs	Bisphosphonates
CI	Confidence Interval
eCRF	Electronic Case Report Form
EU	European Union
FAS	Full Analysis Set
HCP	Health Care Professional
IEC	Independent Ethics Committee
IVRS	Interactive Voice Response System
IRB	Institutional Review Board
IV	Intravenous
MCR	Medication Coverage Ratio
MMAS-8	Morisky Medication Adherence Scale 8-Item
OP	Osteoporosis
PMO	Postmenopausal Osteoporosis
PRO	Patient Reported Outcome
Q6M	Once every 6 months
RCT	Randomized Clinical Trial
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SF-12	Short Form 12

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1. OBJECTIVES

The objective of this observational study is to describe medication-taking behavior of patients treated with denosumab (Prolia®) for postmenopausal osteoporosis (PMO) at 12 and 24 months, using different specific measures (including persistence, adherence and medication coverage ratio). In addition, the study will provide the ability to assess medication-taking behavior in pre-defined subgroups of interest. The study also aims to describe the profile of patients treated with Prolia® for PMO in Germany, Austria, Greece and Belgium. Safety of patients administered Prolia® in an observational setting will be monitored.

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 (National Institute of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2000). Osteoporosis is a major public health threat; in a recent review, 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 (Kanis et al, 2005; Cree et al, 2003). About 40% to 50% of women are at risk of having an osteoporotic fracture in their lifetime (Dennison et al, 2006). In 2000, the number of osteoporotic fractures in Europe was estimated at 3.79 million, of which 0.89 million were hip fractures (Kanis and Johnell, 2005).

2.2 Prolia® Background

Denosumab (Prolia®) is a fully human monoclonal antibody that inhibits RANK Ligand (RANKL), a key regulator of osteoclast differentiation, activation and survival. It can bind and neutralize the activity of human RANKL similar to the action of endogenous osteoprotegerin (OPG). Denosumab (Prolia®) has been studied for the prevention and treatment of OP in postmenopausal women. Administration of denosumab 60 mg subcutaneously every six months (SC 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). Denosumab 60 mg SC Q6M (Prolia®) has been approved in all 27 European Union (EU)

member states plus Norway, Iceland and Liechtenstein for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

2.3 Rationale

Osteoporosis can be treated effectively by inhibitors of bone turnover, such as bisphosphonates (BPs), or by anabolic agents, such as parathyroid hormone analogues (Papapoulos and Makras, 2008). Clinical studies have demonstrated the efficacy of the BP class of drugs in reducing the risk of osteoporosis-related fractures (Papapolous et al, 2005). However, difficult dosing regimens (eg, taking medication on an empty stomach in the morning and staying upright for at least 30 minutes), suboptimal patient satisfaction and medication side-effects may limit drug adherence (Sambrook and Cooper, 2006).

Varying terminology is used to describe the extent to which patients adhere to treatment (eg adherence, compliance, persistence) (Cramer et al, 2008). Although the different terms are often used interchangeably, adherence is a general term encompassing both compliance and persistence (Lekkerkerker et al, 2007). Compliance is defined as the extent to which patients act in accordance with the prescribed interval and dose of a given treatment regimen whereas persistence is defined as the cumulative time from initiation to discontinuation of therapy. Adherence is often quantified as medication possession ratio (MPR). It indicates the proportion of days the patient had an adequate supply of the medication, for a given time interval. Although MPR is a widely used measure for adherence of oral medication, there is limited information measuring MPR with injectables (Shi et al, 2007). Indeed, with injectables, the patient is administered the injection and as such would be covered for a specific period of time. Hence, similar to MPR, one can derive the medication coverage ratio (MCR) that measures the proportion of days, the patient has been covered with respect to the medication over a given time interval after receiving the injection.

Poor adherence has been associated with 16-35% increased fracture risk and 37% increased rates of hospitalization and resource use (Huybrechts et al, 2006). With respect to fractures, a recent systematic review (Siris et al, 2009) of 17 observational studies concluded that an increased risk of fracture with poor adherence to medication for osteoporosis may be observed, independent of type of treatment or fracture location. These analyses suggest that long-term persistence with an effective medication may reduce fracture risk.

Suboptimal persistence and adherence with BP therapy in osteoporotic patients have been evaluated in routine clinical care setting. A systematic review and meta-analysis of 24 observational adherence studies (Kothawala et al, 2007) concluded that between one-third and one-half of patients do not take their medication as directed, and non-adherence occurs shortly after treatment initiation. A German retrospective cohort analysis provided evidence of poor adherence in patients with osteoporosis receiving oral bisphosphonate therapy (Hadji et al, 2011). It was demonstrated that a high proportion of patients discontinued/switched oral BP regimens during the first year, and there was an indication that persistence increases with reduced frequency of the administration. However, with a 1-year persistence of monthly oral BP of 30%, the level remains suboptimal (Hadji et al, 2011). In one study, compliant patients receiving oral BP therapy were shown to have a decreased risk of fractures compared with those who are non-compliant (Hadji et al, 2011).

A study using health insurance outpatient claims in Germany reported that only about 35% of patients treated with Q3M intravenous (IV) BPs remain on the treatment after the first year. A limitation in this study was that these IV BP-treated patients had poorer prognosis and a shorter life expectancy compared with users of oral BPs (Hoffmann et al, 2008). Hence, characteristic of patients being treated is central to type of observed persistence. The German Retrospective Cohort Analysis (GRAND) on non-adherence in osteoporosis showed that the rate of patients receiving appropriately scheduled follow-up administration of IV bisphosphonate is estimated to be similar to the 1-year persistence with oral BPs (Hadji et al, 2011). In general, longer dosing intervals are thought to contribute to better treatment adherence and persistence (Warriner and Curtis, 2009). Therefore Prolia® (denosumab) administered every 6 month (Q6M) as an SC injection might result in better treatment adherence and persistence than weekly or monthly oral BP treatment regimen. The DAPS (Denosumab Adherence Preference and Satisfaction, study number 20060232) study, a multicenter, randomized, open-label, 2-year, crossover phase 3 study in 250 women with osteoporosis, showed that subjects treated with Prolia® (denosumab) had significantly reduced rate of non-adherence (by 58%) and non-persistence (by 54%) as compared with weekly alendronate at 12 months (Kendler et al, 2011). The study also showed that patient ratings for treatment necessity, preference and satisfaction were significantly greater for Prolia® (denosumab) and ratings for treatment bother were significantly greater for alendronate (Kendler et al, 2011).

While these data help support the contention for use of longer dosing intervals in treatment of osteoporosis, preference and adherence information in DAPS was collected in a randomized clinical trial (RCT) setting, which may not necessarily reflect what occurs in daily routine clinical practice. In RCTs, patients are followed and treated in a highly structured environment following a defined protocol. Therefore, there is interest in evaluating adherence and persistence in observational (non-interventional) studies that more closely reflect daily clinical practice (Lekkerkerker et al, 2007). However, participation in any prospective study (both RCTs and observational studies) affects patients' behavior (Hawthorne effect), which will potentially affect the outcome, resulting in increased adherence and persistence levels. Also, again as with any prospective study, selection (due to the need of consent and/or due to practical constraints) of both participating physicians and participating patients could affect the study generalizability. However, keeping a log of potential participating physicians and patients would help put the study results into appropriate context.

Further, while approaches for measuring persistence and compliance for oral medications in PMO population are well documented in the literature, at present very little information and no widely-accepted definition is available regarding the measurement and/or the level of adherence for non-oral and less frequently administered medications such as (yearly, Q3M) IV BPs. The distinction between persistence (continuous use of the medication) and compliance (taking the medication as prescribed/recommended) can be marked for oral medications. However, for an injectable medication, compliance component may be less an issue (ie, it is unlikely that an injection will not be taken as prescribed, particularly if administered by a healthcare professional (HCP)). To mark this particularity, we use the concept of medication taking behavior as an umbrella definition encompassing adherence, persistence and MCR for an injectable drug like Prolia®. Hence, by using different specific measures each capturing an aspect of patient's medication-taking behavior, this observational study makes it possible to explore ways of capturing adherence for Prolia® in a routine clinical practice setting.

The current study is being performed to describe Prolia® patients' medication-taking behavior (including persistence) in a non-interventional routine clinical care setting. In addition, data from this trial will also complement data generated by the POSSIBLE EU® study, an observational longitudinal cohort study on postmenopausal women in 5 countries in Europe receiving bone loss medications (Freemantle et al, 2010).

In addition, safety of patients administered Prolia® in a routine clinical setting also will be monitored by collecting adverse drug reactions and serious adverse drug reactions in postmenopausal women administered Prolia® as part of their normal clinical care.

Also, this prospective study being conducted in routine clinical practice will enable collection of patient characteristics and factors affecting with medication-taking behavior associated with Prolia® therapy.

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

2.4 Clinical Hypotheses

The study is descriptive in nature, and a formal hypothesis will not be tested in this observational study. However, different specific measures of medication-taking behavior (including persistence, adherence, medication coverage ratio) with Prolia® at 12 and 24 months will be estimated.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multi-center, international, observational study in women with postmenopausal osteoporosis who receive denosumab (Prolia®) Q6M, SC according to the applicable approved Prescribing Information (eg, EU Summary of Product Characteristics (SmPC) or equivalent) for the treatment of PMO in routine clinical practice. As per definition, apart from being asked to voluntarily complete two short questionnaires on enrollment day (baseline), this observational study will not alter the routine clinical management of patients. Patients enrolled into this study will not be required to perform any other additional assessments (laboratory or diagnostic) for the specific purposes of the study.

Patients will be eligible to enroll within 4 weeks after administration of their first Prolia® injection. The physician's decision to treat the patient with Prolia® must precede patient's consent to take into the study. However, the decision to treat with Prolia® or to prescribe Prolia®, the first Prolia® injection, obtaining the appropriate written informed consent (as required per local country regulations) and the subsequent enrollment to the study can happen at the same visit to avoid extra subject visits and to avoid interfering with country specific routine clinical practice. The Prolia® treatment decision must happen independently of study considerations and before enrollment into the study (maximum 4 weeks from first injection). Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the

potential study candidate (eg, date of screening). Investigators will also document the patient participation rates in the study at their sites. Patients are expected to receive their scheduled Prolia® injection every six months at the investigator sites as part of her routine clinical care. All data recorded will be collected per routine clinical practice including adverse drug reactions and serious adverse drug reactions. The overall study design is described in a study schema at the end of the protocol synopsis section.

Approximately 1500 postmenopausal patients administered denosumab 60 mg Q6M SC Prolia® for osteoporosis (600 in Germany and 300 in Austria, Greece and Belgium) will participate across about 170 sites in Germany, Austria, Greece and Belgium. Enrollment in each country is expected to last approximately 12 months. Countries will start recruiting at different times and are expected to recruit at different rates. Patients will be followed for a period of 2 years after study enrollment.

Study objectives include describing persistence with Prolia® at 12 and 24 months. Given the 6 monthly administration frequency of Prolia®, a 24-month observation period is considered adequate to reliably ascertain persistence endpoints and capture relevant details around patient medication-taking behaviors in routine clinical practice.

The study also will describe the profile of patients treated with Prolia® for osteoporosis and ascertain the predictors of persistence to Prolia®, considering WHO (2003) 6 dimensions:

- Therapy related
- Condition related
- Patient related
- Physician related
- Health care system related
- Socio-demographic related

Details on the covariates can be found in Section 10.1.3.

Baseline characteristics including health status will be evaluated using the Short Form (SF-12) generic health-related quality of life instrument. SF-12 is a 12-item survey, with each item assessing broad measures of health status, and all 12 items adding up to 2 summary scales: Physical Component Summary (PCS) and Mental Component summary (MCS) scores.

Other baseline characteristics to be captured from the patient include:

- Self-reported medication taking behavior with prior osteoporosis therapy
- Health care insurance (private or public)

Only adverse drug reactions and serious adverse drug reactions will be recorded in the study, consistent with the guidance for observational studies.

Additional information, as outlined in Appendix A, will be collected over the routine clinical visits over a period of up to 2 years.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

The study will be conducted in approximately 170 representative (country specific) sites (60 in Germany and 30 each in Austria, Greece and 50 in Belgium). Additional sites may be added or removed as deemed necessary to ensure enrollment of the target number of patients. After feasibility, sites selected will represent those providing overall PMO care in each country and region, with regards to type and location of site. Sites that do not enroll patients within 2 months after site initiation may be closed. Sites will be selected from the available list of potential sites in the country, following feasibility checks. The selection will be stratified by the country and main site characteristics (size, public/private and/or specialty).

3.3 Number of Subjects

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

Approximately 1500 patients (about 600 in Germany and 300 each in Austria, Greece and Belgium) will be enrolled into the study. The justification for the sample size is provided in Section 10.2.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The enrollment period is expected to last approximately 12 months in each country. Patients providing appropriate written informed consent and fulfilling inclusion and exclusion criteria will be eligible to enroll in the trial. Enrolled patients will have a follow-up period of up to 24 months after enrollment in the study.

3.4.2 End of Study

End of study is defined as the date that the last patient enrolled completes up to 24 months of observation or when the last patient in the study ends their participation in the study.

4. SUBJECT ELIGIBILITY

Postmenopausal women with OP who receive an injection of Prolia® according to the approved Regional Prescribing Information (eg, EU SmPC) and who meet the inclusion/exclusion criteria will be eligible to participate in the study.

Investigators will be expected to maintain a screening log with limited information on all potential study candidates (eg, date of screening). Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 Indicated for treatment of OP in postmenopausal women at increased risk of fractures according to the approved Regional Prescribing Information (eg, EU SmPC in Germany, Austria, Greece and Belgium).

4.1.2 Enrolled into the study within 4 weeks of receiving their first injection of Prolia® according to the approved Regional Prescribing Information (eg, EU SmPC in Germany, Austria, Greece and Belgium).

4.1.3 Appropriate written informed consent has been obtained (as required per local country regulations).

4.2 Exclusion Criteria

4.2.1 Patient is currently enrolled in or has been enrolled within the prior 6 months in a study involving any investigational procedure, device or drug.

4.2.2 Contraindicated for treatment with Prolia® according to the approved Regional Prescribing Information (eg, EU SmPC in Germany, Austria, Greece and Belgium).

4.2.3 Participation in ongoing or previous denosumab clinical trials.

4.2.4 Patient has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the patient to give written informed consent.

5. SUBJECT ENROLLMENT

Before patients may be entered into the study, Amgen requires a copy of the site's written Independent Ethics Committee (IEC) or Independent Review Board (IRB) approval of the protocol as applicable, informed consent form (as required by local country requirements) and all other patient information and/or recruitment material (see Section 11.2).

All patients or their legally acceptable representatives must personally sign and date an appropriate consent form (as required per local country regulations) before being enrolled into this study.

Enrollment is defined as the date the patient is enrolled in the study via an Interactive Voice Response System (IVRS). All patients who are enrolled will be assigned a unique 11-digit patient identification number before the observation period commences. Patient ID numbers will be assigned in sequential order within a site beginning with 126XXXXX001, with 'XXXXX'=site number. 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 administered Prolia® in routine clinical practice. No study-specific treatment will be provided, and apart from being asked to complete (optional) two short questionnaires on enrollment day (baseline), and provide information on health care provider (public or private), no additional clinical procedures or assessments will be required as part of this observational study.

Patients will be observed for a period of up to 2 years after their entry in the study. Patients who switch to another therapy or discontinue treatment will not be followed up.

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 as per SmPC.

7. STUDY PROCEDURES

With the exception of completing optional questionnaires on enrollment day (baseline), there are no study specified procedures or changes to routine clinical management of patients required as part of this protocol. Based on eligibility criteria, patients will be invited to participate in the study when they visit the site for a routine appointment as part of their standard care. It is anticipated that patients will return to the clinic every 6 months to receive their Prolia® injection. At the conclusion of each visit, the physician

or designated study personnel will record individual patient data on the eCRF. Clinical information obtained for routine clinical practice will be recorded, if available, including Prolia® administration date, previous PMO therapy, concomitant therapies, medical history (including fracture), serious and non-serious adverse drug reactions and co-morbidities (see Appendix A for Information to be Obtained During Routine Clinical Practice).

Patients will be observed for 2 years following their study enrollment and each site needs to be able to continually follow up patients for this duration, with access to medical notes, to ensure all data, including date of injection, can be obtained.

Patient-related information will also be collected from the prescribing physician or designated study personnel.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to her 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 (or a legally acceptable representative) request or decide to withdraw from the study, all efforts 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 eCRFs.

8.2 Replacement of Subjects

Patients who withdraw from the study or lost to follow-up will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

In this observational study, only adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) will be collected and reported.

General information regarding reporting of ADRs:

- **Report only AEs/ADRs, other safety findings, or product complaints involving Amgen products**
- **Do not report ADRs that occurred prior to a subject/patient taking an Amgen product**

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE 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 AE includes:

- **Worsening of a pre-existing condition**
- **Events occurring from a medication error or overdose of a product(s), whether accidental or intentional**
- **Events occurring from abuse of a product(s)**
- **Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)**
- **Any lack or loss of intended effect of the product(s)**

9.1.1.1 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

9.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- **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.

9.1.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen

9.1.3 Definition of Other Safety Findings

Other Safety Findings include:

- **Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an ADR and/or SADR**
- **Pregnancy and lactation exposure regardless of whether associated with an ADR and/or SADR**
- **Transmission of infectious agents regardless of whether associated with an ADR and/or SADR**
- **Reports of uses outside the terms for authorized use of the product including off label use when associated with an ADR and/or SADR**

9.1.4 Definition of 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. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints <u>may</u> include but are not limited to issues related to:

- **Appearance (eg, broken, cracks, color, particles, odor)**

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

9.2 Reportable Events and Reporting Timeframes

The Investigator is responsible for ensuring that all ADRs, SADRs, product complaints and other safety findings for Amgen product(s) observed by the Investigator or reported by the patient that occur after the first dose of Prolia® through the final study visit are recorded in the patient's medical record and are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Error! Reference source not found. for a sample Adverse Drug Reaction Report Form and Appendix C for sample Pregnancy and Lactation Notification Worksheets. Refer to Error! Reference source not found. for the reporting timeframes for reportable events.

Table 1. Reporting Timeframes for Reportable Events

Report Type	Description	Reporting Timeframe
SADR	Initial or follow-up for SADRs	Within 1 business day of awareness
Product complaints	Initial or follow-up of all product complaints	Within 1 business day of awareness
Pregnancy and/or Lactation	Initial or follow-up for all pregnancies or lactation occurring in females while taking Amgen product(s) and/or Initial or follow-up for all pregnancies or lactation occurring in female partners of males taking Amgen product(s)	Within 1 business day of awareness
Other ADR	Initial or follow-up for ADR not meeting serious criteria	Within 60 calendar days of the Investigator's knowledge

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, Adverse Event Summary CRF).

The Investigator is responsible for medical management of patients who experience adverse events from the date of awareness to resolution or stabilization.

Amgen will report ADRs and unlisted SADRs as required to regulatory authorities, Investigators/institutions, and IRBs/IECs or other relevant ethical review board in accordance with Pharmacovigilance guidelines and in compliance with local regulations.

The Investigator is to notify the appropriate Institutional Review Board/Independent Ethics Committee IRB/IEC or other relevant ethical review board of SADRs occurring at the site and other AE reports received from Amgen, in accordance with local procedures and statutes.

The AE severity grading scale used will be the Amgen adverse event standard grading score. The severity grading scale used in this study is described in Appendix D

10. STATISTICAL CONSIDERATIONS

10.1 Study Outcomes, Subsets, and Covariates

10.1.1 Study Outcomes

The medication-taking behavior outcome measures are defined below based on the notions of persistence, adherence and MCR.

Persistence (yes/no) with Prolia® at 12 months:

- A patient will be considered persistent with Prolia® at 12 months if patient receives at least 1 Prolia® injection following the first injection no more than 6 months + 8 weeks (ie, no greater than 239 days apart)

Persistence (yes/no) with Prolia® at 24 months:

- A patient will be considered persistent with Prolia® at 24 months if the patient received at least 3 Prolia® injections following the first injection, and the length of time between any 2 consecutive Prolia® injections does not exceed 6 months +8 weeks (ie, no greater than 239 days apart).

Additionally, persistence at 12 and 24 months will also be calculated based on the following windows between injections:

- 6 months +4 weeks (211 days apart)
- 6 months +6 weeks (225 days apart)
- 6 months +12 weeks (267 days apart)

Adherence (yes/no) with Prolia® at 12 months:

- Patients receiving at least 1 Prolia® injection over the 12-month period following the first dose, with the time between the 2 consecutive injections at most 6 months +/- 4 weeks (between 155 and 211 days) apart.

Adherence (yes/no) with Prolia® at 24 months:

- Patients receiving at least 3 Prolia® injections over 24-month period following the first dose, with the time between any 2 consecutive injections at most 6 months +/- 4 weeks (between 155 and 211 days) apart.

Additionally, adherence will also be calculated based on the following windows between injections:

- 6 months +/- 6 weeks (between 141 and 225 days) apart
- 6 months +/- 8 weeks (between 127 and 239 days) apart
- 6 months +/- 12 weeks (between 99 and 267 days) apart

MCR:

- MCR at 12 months is defined as the accumulative number of days covered with Prolia® treatment during the first 12 months divided by 365 days [(365 minus the number of days of missed coverage)/365*100]. It is assumed each injection of Prolia® treatment provides 6 months of coverage from the date of injection up until the date of the next injection.
- MCR at 24 months is defined as the accumulative number of days covered with Prolia® treatment during the first 24 months divided by 730 days [(730 minus the number of days of missed coverage)/730*100].

Other observational study outcomes are:

Time to non-persistence over 24 months:

- For each of the 4 definitions of persistence at 24 months, time to non-persistence for non-persistent patients is calculated as the time in days between the date of the first Prolia® injection and the date of last Prolia® injection received during the period where the patient is still classified as persistent, according to the corresponding definition of persistence, plus 6 months (183 days).

Number of Prolia® injections within the specified window over 24 months:

- For each of the 4 definitions of persistence at 24 months, the number of Prolia® injections within the specified window (defined in the persistence definition) is the

number of injections that a patient took during the 2-year period and that were given within the appropriate window from the previous injection, irrespective of when the previous injection was given. Possible values are 0, 1, 2 or 3 injections (the definition does not apply to the first injection).

Safety outcomes:

- Incidence of serious and non-serious ADRs

10.1.2 Analysis Sets

The Full Analysis Set (FAS) will consist of all enrolled patients satisfying the inclusion/exclusion criteria who receive at least one Prolia® injection and have a non-missing enrollment date. All analyses will be performed using the FAS.

10.1.3 Subsets and/or Covariates

For selected medication-taking behavior outcomes (persistence and adherence), summary statistics will be provided for each of the following covariates of interest within each country.

Collection of the covariates will not be mandatory. They will be collected where information can be obtained during routine clinical practice and wherever local country regulations allow it and data are available. As the analyses will be done by country, the impact of missing variable at a country level should be minimal.

Therapy related:

- Patients PMO support tools and/or programs categories (Category 1, 2 and 3):
    1. Patients who will not use any patient support tools and are not registered to any active reminder system (Category 1)
    2. Patients who will be using at least 1 passive patient support tool (eg, next appointment card, bone passport, sticker from the packaging, etc.). These patients should not have registered to any active reminder tool/system (Category 2)
    3. Patients who will use one of the available active reminder systems and who will be receiving a reminder for the next Q6M injection by email, phone call, text message etc (Category 3)

Condition related:

- Body mass index (≤ 25 or > 25 kg/m^2)
- Age at menopause (years)
- Time since the most recent previous fracture to first injection (< 12 months or ≥ 12 months)
- Previous fracture (yes/no)
- Previous hip fracture (yes/no)

- Previous vertebral fracture (yes/no)
- ≥ 2 Previous fractures (yes/no)
- Previous hospitalization for osteoporotic fracture and/or surgical osteoporotic fracture treatment
- Parent fractured hip (yes/no)
- Current smoker (yes/no)
- Former smoker (yes/no)
- Systemic glucocorticoids (yes/no)
- Secondary osteoporosis (yes/no)
- Alcohol 3 or more units per day (yes/no)
- Femoral neck BMD T-score (if available) (≤ -2.5 or > -2.5)
- Lumbar spine BMD T-score (if available) (≤ -2.5 or > -2.5)

Patient related:

- Age group (< 65, ≥ 65 to <75, ≥ 75 years)
- Information on PMO diagnosis according to the World Health Organization (WHO) Classification, including bone mass measurements and date if available
- Date of postmenopausal osteoporosis diagnosis (month and year)
- Number of prescription medications taken at baseline
- Exposure to prior prescription osteoporosis therapy (yes/no)
- Calcium and/or Vitamin D supplementation at baseline (yes/no)
- History of discontinuation of prescription osteoporosis therapy (yes/no)
- Prior prescription of PMO therapy during the last 12 months prior to enrollment
- Self-reported medication-taking behavior with prior osteoporosis therapy

Patient reported outcomes:

- SF-12 physical component summary score at baseline
- SF-12 mental component summary score at baseline
- MMAS-8 summary score at baseline.

Number and type of selected co-morbidities, over the 12 months prior to enrollment, including the following:

- Anemia or other blood disease
- Back pain
- Cancer (not considered cured)
- Depression
- Other mental illness
- Diabetes (Type 1 or 2)

- Endocrine disease (eg, thyroid, adrenal, or pituitary)
- Hearing impairment (very hard of hearing, even with hearing aids)
- Hypertension
- Myocardial infarction
- Stroke
- Peripheral vascular disease
- Heart disease (excluding hypertension, myocardial infarction, stroke, and peripheral vascular disease)
- Historical spine/hip/leg fracture
- Kidney disease
- Liver disease including gall bladder conditions
- Lung disease
- Neurological disease (such as multiple sclerosis or Parkinson's)
- Obesity (body mass index > 30 kg/m2)
- Osteoarthritis, degenerative arthritis
- Rheumatoid arthritis
- Other rheumatologic diseases (excluding osteoarthritis, degenerative arthritis, and rheumatoid arthritis)
- Gastrointestinal disorders (such as ulcers or gastritis)
- Visual impairment (such as cataracts, glaucoma, macular degeneration)
- Genitourinary disease (such as problems with uterus or ovaries)
- Alcohol or drug problems

Physician related:

- Type of prescribing HCP (Physician specialty: Primary Care Provider vs. Specialist care - Orthopedist, Trauma Surgeon, Surgeon, Rheumatologist, Internist, Endocrinology, Rehabilitation Medicine, Geriatrician, Obstetrician/Gynecologist, Family Physician/General Practitioner, other)
- Physician gender (female or male)
- Physician years of practice (1 to 4, 5 to 9, ≥ 10)
- Physician practice reminder (yes/no)
- Clinical practice type (Private, Health Maintenance Organization, Group Practice, Academia, Other)
- Reason for prescribing Prolia® (OP, established OP, osteoporotic fracture risk factors, other like 'oral PMO BP treatment not possible', 'iv PMO BP treatment not possible' or 'other PMO treatments not possible for patients')
- Size of the clinic (small, medium or large)

Health care system related:

- Type of health care insurance (public/private/other)

Socio-demographic related:

- Educational level (no high school diploma, high school diploma, college degree or above)
- Patient living situation
- Patient employment status
- Marital status (married, never married, divorced/separated, widowed)
- Proximity to clinic/practice
- Geographic region
  - Country: Germany, Austria ,Greece or Belgium
  - Rural vs. urban

10.2 Sample Size Considerations

Approximately 1500 patients will be enrolled in this study, about 600 in Germany and 300 each in Austria, Greece and Belgium.

Since this is an observational study with descriptive objectives, the sample size proposed was based on the level of precision (ie, half-width) of the 95% confidence interval (CI) around the point estimates of the categorical measure of medication-taking behavior (persistence and adherence) with Prolia® at 12 and 24 months, overall, at the country level and within the country's selected covariates of interest.

The main covariates of interest within each country are: age group (75+), enrollment in PMO support tools or programs (if available), prescribing HCP, patient exposure to prior osteoporosis therapy, patient prior history of discontinuing osteoporosis therapy, number of selected co-morbidities and co-medications at baseline and baseline MMAS-8 (Morisky et al, 1990) and SF-12 (Ware et al,1998) scores. A complete and more detailed list of the covariates and their categorization will be provided in the Statistical Analysis Plan (SAP).

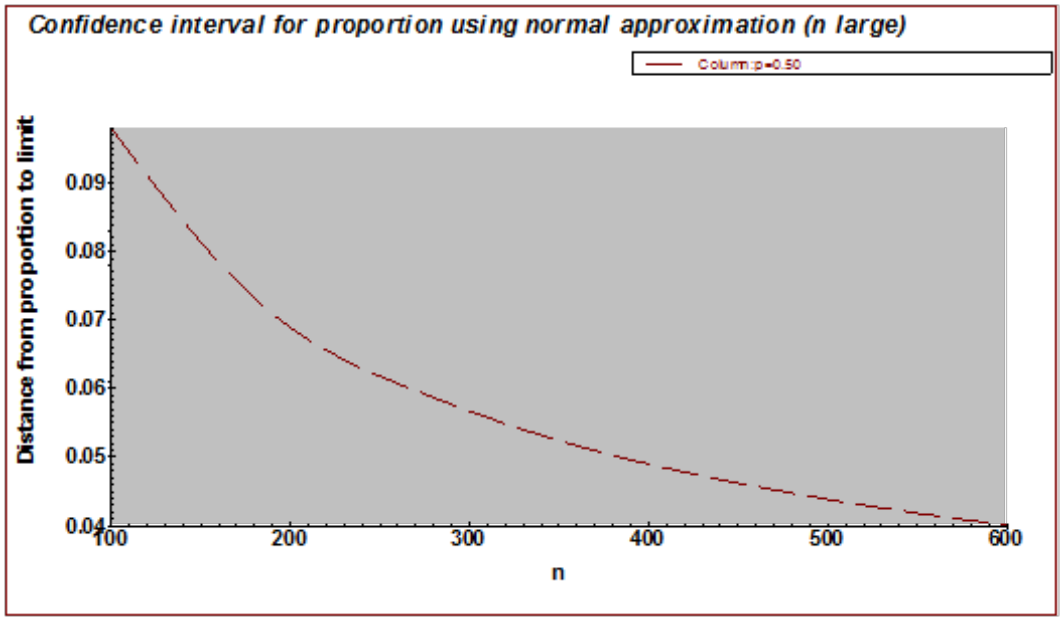
Sample Size per Country:

The half width of the 95% CI around the rate estimate varies from at most 9.8% to 5.7% when the sample size ranges from approximately 100 to 300, as shown below. Because the gain in precision as the sample size doubles to 600 is relatively small (from 5.7% to 4.0%), the minimum sample size per country is proposed to be 300 patients.

The sample size is also determined to capture the country diversity in population and medical practices and to provide enough patients to describe the characteristics of patients administered Prolia® for postmenopausal osteoporosis in each country.

Based on previous clinical trial experience in each country and given the diversity of sites and patients in Germany the following number of sites per country and a sample size of approximately 10 patients per site are proposed: For Austria and Greece, about 30 sites at each country and about 50 sites in Belgium will be selected to provide the minimum sample size of approximately 300 patients per country. For Germany, about 60 sites will be selected across the different regions to provide a sample of approximately 600 patients.

Figure 1. Half-width of the 95% Confidence Interval – Country Sample Size



An overall sample size of approximately 1500 patients will allow rate estimation to Prolia® at each time point with sufficient precision such that the half-width of the 95% CI for the persistence rate would be no larger 2.8%.

Please note that the definitions of medication-taking behavior apply to all patients, whether they withdraw, are lost-to-follow up or complete the study. Therefore all patients in the full analysis set will be included in the point estimates of the categorical measures of medication-taking behavior and no replacement of patients is proposed.

Sample Size per Country and Subgroups:

The table below provides the half-width of the 95% CI for different subgroups of patients. When the subsets vary from 15 to 150 patients, the half-widths of the 95%CI change from 25.3% to 8.0% respectively, nearly halving the width when the sample size increases from 15 (25.3%) to 50 (13.9%). Therefore any subgroup with at least

50 patients (ie, at least 17% of the patients enrolled in Austria, Greece or Belgium, or 8% of the patients enrolled in Germany) will have a half-width of the 95% CI of at most 13.9%.

The number of patients in the subgroups determined by the covariates cannot be predicted in advance, but given that most covariates are dichotomous, it is expected that most subgroups will have at least the minimum number discussed above and that the 95% CIs will show a half width of at most 13.9%, when 300 patients are enrolled in Austria, Greece and Belgium respectively, and 600 in Germany.

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

Number of Subjects in Subgroup	Half-Width of the 95% Confidence Interval (%)
15	25.3
20	21.9
25	19.6
30	17.9
35	16.6
40	15.5
45	14.6
50	13.9
100	9.8
150	8.0
300	5.7
600	4.0
1200	2.8
1500	**2.5**

Half-widths were calculated assuming that the persistent rate is 50%.

10.3 Interim Analysis and Early Stopping Guidelines

An initial reporting of baseline data will be conducted for each country once the target enrollment for the country is completed and the baseline data has been cleaned. This reporting of baseline data is planned to allow publication of the data pertaining to the population of subjects who are choosing to initiate treatment with Prolia.

Moreover, an interim analysis by country is planned to ascertain the persistent rate with Prolia® treatment at 12 months, overall and for selected subgroups defined by covariates of interest. Since the persistent rate at 12 months only involves the first 2 Prolia®

injections, the interim analysis can be conducted when all patients have had the opportunity to receive their second Prolia® injection within the allowable window for persistence (6 months plus 12 weeks from the initial Prolia® injection). Any data collected after this date will not be included in the interim analysis. This interim analysis is planned to proactively inform reimbursement authorities if needed.

The design of the study will not change based on the initial baseline reporting or the interim analysis results. No stopping rules will be applied due to the observational nature of this study.

The exact timing of the initial baseline reporting and the interim analysis for each country will be defined to allow prompt and efficient reporting, as data becomes available.

10.4 Planned Methods of Analysis

10.4.1 General Approach/Considerations

This is an observational study for which the analysis will be descriptive in nature, and a formal hypothesis will not be tested.

In general, data summaries will be presented overall and by country.

Frequency distributions will be described for categorical outcomes. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values.

Baseline characteristics of the patients (patient disposition, demographic and baseline characteristics including patient reported questionnaires) will be summarized using descriptive statistics and compared across countries to identify possible differences. Missing covariate information will be compared as well across countries to identify potential sources of heterogeneity.

10.4.2 Analysis of Key Study Outcomes

10.4.2.1 Effectiveness Outcomes

Medication-taking behavior outcome:

For the categorical measures of medication-taking behavior (persistence and adherence) and each of the proposed windows, the number and percentage of patients satisfying each of the medication-taking behavior outcomes at 12 and 24 months will be summarized overall and by country, and the associated 95% confidence intervals will be presented. Similarly for the MCR outcome at 12 and 24 months, mean estimates and the associated 95% confidence intervals will be presented.

For each medication-taking behavior outcomes, summary statistics will be provided also by country and covariates of interest. In addition, univariate logistic regression will be used to explore the association of each pre-specified covariate with selected medication-taking behavior at 24 months (persistence and adherence). For each covariate entered individually in the model, point estimates of the odds ratio, and 95% confidence intervals will be provided for each pairwise comparison relative to the reference group (to be determined in the SAP).

Moreover, a multivariate logistic regression including selected covariates that showed possible association with persistence from the univariate analyses at 24 months will also be performed to identify predictors of selected medication-taking behavior to Prolia® at 24 months. A stepwise model selection will be implemented using the SAS LOGISTIC procedure.

Time to non-persistence:

Summary statistics of the time to non-persistence will be provided including only non-persistent patients at 24 months. Furthermore, time to non-persistence will be summarized by Kaplan-Meier methodology including all patients. The median, Q1 and Q3 time (months) to non-persistence will be presented as well as the number of patients who did not persist with Prolia® at 12, 18 and 24 months. Time to non-persistence for those patients who persisted with Prolia® treatment during the 24 months or up to the analysis cutoff date, will be censored at the study day associated with the date of the last Prolia® injection plus 6 months (183 days). Otherwise, patients will be considered non-persistent at the study day defined by the date of last injection received while the patient is still classified as persistent plus 6 months (183 days).

Because it is expected that some patients may change practice during treatment but continue with treatment, sensitivity analysis is proposed to account for the patients that are lost to follow-up. For those patients who changed practice and may have continued treatment elsewhere, the analysis above will be repeated censoring those patients that persisted while on study but were lost to follow-up afterwards, ie, did not return to the clinic after their last Prolia® injection and were identified as being lost to follow-up on the appropriate eCRF by the investigator prior to the analysis cut-off date. Similarly, patients who died but were persistent while on study will also be censored in this sensitivity analysis. These lost to follow-up patients and those who died will be censored at the date of last injection received during the period where the patient is still classified as persistent plus 6 months (183 days).

Number of injections received within the allowable window over 24 months:

Summary statistics of the total number of Prolia® injections received within a window from the previous injection (independently of the time the previous injection was taken) will be provided over the 24-month period. Categorical summaries will be produced of the number and proportion of patients with a total of 0, 1, 2, or 3 Prolia® injections within the required timeframe.

10.4.2.2 Safety Outcomes

All serious and non-serious ADRs to Prolia® will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Patient incidence of serious and non-serious ADRs leading to discontinuation of Prolia® and serious ADRs associated with fatal outcomes, will be tabulated by system organ class and preferred term.

The number of Prolia® injections administered will be summarized.

10.4.3 BMD Analysis

Bone mineral density and related T-score will be tabulated. Change in BMD will also be summarised when a patient provides a baseline and post baseline measurement at the same location using the same machine. BMD values will be collected if and when BMD is assessed by DXA during the study as per local clinical practice and or guidelines.

10.4.4 Additional Analyses

Further analyses may be specified in the SAP.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

This observational study will comply with all relevant national requirements on a country-by-country basis. The following is applicable per local country regulations.

An initial generic informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a patient's participation in the observational non-interventional study, the investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

The investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the investigator shall inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the investigator will be acting in that capacity, the investigator should document such in the patient's medical record. The acquisition of informed consent and the patient's agreement or refusal of her notification of the primary care physician 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.

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of patients into the study.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

Where applicable, the investigator will be responsible for obtaining annual IEC/IRB approval/renewals throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the patient's confidentiality is maintained:

- On the eCRFs or other documents submitted to Amgen, patients should be identified by a patient identification number only, with a year of birth on the demographics eCRF as permitted per local country regulations.
- For SADRs reported to Amgen, patients should be identified by their initials and a patient identification number only.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB 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 named representatives to have access to her study-related records, including personal information, without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12.2 Study Documentation and Archive

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

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

In this study, an electronic system (eg, IVRS) will be used for tracking patient enrollment and withdrawal. The site study team will be required to enter site and patient identifiers and some patient demographics into this system in order to enroll a patient into the study.

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 should include:

- Patient files containing completed eCRF, informed consent forms and patient identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation, and all correspondence to and from the IEC/IRB 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.

12.3 Study Monitoring and Data Collection

The Amgen representative 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, eCRFs and other pertinent data) provided that patient confidentiality is respected.

The Amgen monitor is responsible for verifying the eCRFs 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 monitor should have access to patient medical records and other study-related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the 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 (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs 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 will be performed on patient data received at Amgen. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be 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 will be created in the electronic data capture (EDC) system database for site resolution and closed by Amgen reviewer.
- The clinical site investigator signs only the Investigator Verification Form for this EDC study. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF, 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, race, 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.

12.4 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.5 Publication Policy

The results of this study are intended for publication. It is envisioned that a manuscript will be prepared for submission to a peer-reviewed journal. The choice of target journal will be considered in consultation with the authors. In addition, one or more abstracts may be prepared for submission to relevant scientific congresses.

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal 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 should 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 corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.6 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. If permitted under applicable regional laws or regulatory guidelines, patients may be compensated for other inconveniences not associated with study-related injuries (eg, completion of questionnaires).

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14. APPENDICES

Appendix A. Schedule of Data Collection

Data (as available)	Baseline	Follow-up Data[a]	M24, End of Study or Early Termination
Informed consent (or equivalent as required by local regulations)	X		
Therapy related data, such as type of PMO support tools and/or programs	X		X
Condition related data, including fracture history, menopause information, BMI, smoking, alcohol, bone mineral density	X		
BMD data		X	X
Patient related data, such as PMO history, including date of diagnosis, previous PMO therapy, date of PMO diagnosis	X		
Physician-related data, such as type of prescribing HCP	X		
Medical history (selected co-morbidities)	X		
Health care related	X		
Patient socio-demographic factors	X		
Physical examination	X	X	X
Concomitant medication	X	X	X
Calcium and vitamin D supplements	X	X	X
Prolia® administration information (injection dates)	X	X	X
Non-serious and Serious Adverse Drug Reactions		X	X
New clinical fracture summary		X	X
SF-12 quality of life instrument (PRO)[b]	X		
MMAS-8 questionnaire (PRO)[b]	X		
Reason(s) for discontinuation of therapy with Prolia®		X	X
Reason and type of treatment if switched from Prolia® treatment		X	X

[a] All data recorded will be collected during routine clinical practice at approximately 6 month intervals, where available

[b] Administered at baseline and if allowed per local regulations

Appendix B. Sample Adverse Drug Reaction Report

AMGEN 20110126

Adverse Drug Reaction Report
Notify Amgen of SADRs and Product Complaints Within One Working Day
UK: +44 20 7136 1046

☐ New ☐ Follow-up

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

1. SITE INFORMATION

Site Number	Investigator/Study Doctor	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Initials	Date of Birth Day Month Year OR Age	Sex ☐F ☐M	Race

3. ADVERSE DRUG REACTON, Other Safety Finding or Product Complaint

Adverse Drug Reaction Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Drug Reaction *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Is the event serious? No	Is the event serious? Yes	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by Amgen drug? See section 10 No	Relationship Yes	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal
							✓	
							✓	
							✓	
							✓	
							✓	

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

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject/patient hospitalized? ☐No ☐Yes, If yes, provide date(s) →		

5. SUSPECT AMGEN PRODUCT

	Initial Start Date Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld
Amgen Product: _____ Lot #: _____						
Amgen Product: _____ Lot #: _____						
Amgen Product: _____ Lot #: _____						

6. RELEVANT CONCOMITANT MEDICATIONS (e.g. chemotherapy) If none check here: ☐

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

FORM-015478 Adverse Drug Reaction Report Form v5.0 Effective date: 17-Aug-2012 *ADR Report Form Created: 05-Dec-2012*
Page 1 of 2

AMGEN 20110126	Adverse Drug Reaction Report *Notify Amgen of SADRs and Product Complaints Within One Working Day*	☐New ☐Follow-up
	Site Number / Subject ID Number	

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

8. RELEVANT LABORATORY VALUES *(Include baseline values)* If none check here: ☐

Date (Day Month Year)	Test / Unit										

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* If none check here: ☐

Date (Day Month Year)	Additional Tests	Results	Units

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

Signature of Investigator or Designee	Title	Date

FORM-015478 Adverse Drug Reaction Report Form v5.0 Effective date: 17-Aug-2012 *ADR Report Form Created: 05-Dec-2012*
Page 2 of 2

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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

Appendix D. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

Grade	Amgen Standard Adverse Event Toxicity Grading Scale
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	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.)
5	FATAL

Superseding Amendment 1

Protocol Title: Prospective Observational Study to Evaluate Medication-taking Behavior With Denosumab (Prolia®) and Patient Characteristics in Postmenopausal Women With Osteoporosis in Routine Clinical Practice in Germany, Austria, Greece and Belgium

AMG 162 - Prolia® (Denosumab)

Amgen Protocol Number 20110126

Superseding Amendment 1 Date: **14 December 2012**

Rationale:

The protocol amendment 1 is being superseded to make the safety reporting requirements consistent with new European Union pharmacovigilance directive for non-interventional studies. Typographic and editorial changes were made where necessary.

Description of Changes:

Section: Title page

Add:

Superseding amendment 1: **14 December 2012**.

Section: Global

Replace:

06 September 2012

With:

14 December 2012

Section: 9, Safety Data Collection Recording And Reporting

Replace:

In this observational study, only adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) will be collected and reported.

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial patient. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the patient are recorded in the patient's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

An adverse drug reaction (ADR) is an adverse event that is considered related to the medicinal product.

9.1.2 Reporting Procedures for Adverse Drug Reactions

The investigator is responsible for ensuring that all ADRs to Prolia® observed by the investigator or reported by the patient that occur after the first dose of Prolia® through to

the end of study are reported to Amgen using the applicable eCRF (eg, Adverse Event Summary eCRF).

The investigator must assess whether any adverse event is possibly related to Prolia®. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by Prolia? If indicated yes, the investigator must report the ADR and assign the following ADR attributes:

- ADR diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution,
- Severity (and/or toxicity per protocol), and
- Action taken.

The AE severity grading scale used will be the Amgen adverse event standard grading score. The severity grading scale used in this study is described in Appendix B.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- 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
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

A SADR is a SAE that is considered related to the medicinal product.

9.2.2 Reporting Procedures for Serious Adverse Drug Reactions

The investigator is responsible for ensuring that all SADRs related to Prolia® from the first dose of Prolia® until the end of study are recorded in the patient's medical record and are reported to Amgen via a SADR report form. The SADR form must be submitted to Amgen within 1 working day of discovery or notification of the event.

New information relating to a previously reported SADR must be recorded on an SADR form. All changes to SADR forms must be sent to Amgen within 1 working day of receipt of the new information. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided on the SADR form must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

Amgen will report SADRs as required to regulatory authorities, investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations for observational studies.

The investigator should notify the appropriate IRB/EC/head of the medical institution of SADRs occurring at the site and other SADR reports received from Amgen, in accordance with local procedures and statutes.

Determination of expectedness for Amgen products will be based on the contents of the approved regional prescribing information (eg, EU SmPC in Germany, Austria, Greece and **Belgium**).

9.3 Pregnancy Reporting

Any confirmed pregnancy of a female patient should be reported to Amgen within 1 working day of discovery or notification of the pregnancy. Initial information should be provided using the pregnancy notification worksheet (Appendix C). Follow-up information on the pregnancy outcome should be communicated by the investigator to Amgen Global Safety as soon as available.

With:

In this observational study, only adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) will be collected and reported.

General information regarding reporting of ADRs:

- **Report only AEs/ADRs, other safety findings, or product complaints involving Amgen products**
- **Do not report ADRs that occurred prior to a subject/patient taking an Amgen product**

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE 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 AE includes:

- **Worsening of a pre-existing condition**
- **Events occurring from a medication error or overdose of a product(s), whether accidental or intentional**
- **Events occurring from abuse of a product(s)**
- **Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)**
- **Any lack or loss of intended effect of the product(s)**

9.1.1.1 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

- **It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.**

9.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- **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.

9.1.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen

9.1.3 Definition of Other Safety Findings

Other Safety Findings include:

- **Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an ADR and/or SADR**
- **Pregnancy and lactation exposure regardless of whether associated with an ADR and/or SADR**
- **Transmission of infectious agents regardless of whether associated with an ADR and/or SADR**
- **Reports of uses outside the terms for authorized use of the product including off label use when associated with an ADR and/or SADR**

9.1.4 Definition of 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. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints <u>may</u> include but are not limited to issues related to:

- **Appearance (eg, broken, cracks, color, particles, odor)**
- **Labeling (eg, missing, torn, smudged)**
- **Durability (eg, stability issues)**

- **Open packaging**
- **Device damage (eg, pre-filled syringe with bent needle)**
- **Inability of customer to understand product labeling**
- **Inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe]**

9.2 Reportable Events and Reporting Timeframes

The Investigator is responsible for ensuring that all ADRs, SADRs, product complaints and other safety findings for Amgen product(s) observed by the Investigator or reported by the patient that occur after the first dose of Prolia® through the final study visit are recorded in the patient's medical record and are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Appendix B for a sample Adverse Drug Reaction Report Form and Appendix C for sample Pregnancy and Lactation Notification Worksheets. Refer to Table 1 for the reporting timeframes for reportable events.

Table 1. Reporting Timeframes for Reportable Events

Report Type	Description	Reporting Timeframe
SADR	Initial or follow-up for SADRs	Within 1 business day of awareness
Product complaints	Initial or follow-up of all product complaints	Within 1 business day of awareness
Pregnancy and/or Lactation	Initial or follow-up for all pregnancies or lactation occurring in females while taking Amgen product(s) and/or Initial or follow-up for all pregnancies or lactation occurring in female partners of males taking Amgen product(s)	Within 1 business day of awareness
Other ADR	Initial or follow-up for ADR not meeting serious criteria	Within 60 calendar days of the Investigator's knowledge

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, Adverse Event Summary CRF).

The Investigator is responsible for medical management of patients who experience adverse events from the date of awareness to resolution or stabilization.

Amgen will report ADRs and unlisted SADRs as required to regulatory authorities, Investigators/institutions, and IRBs/IECs or other relevant ethical review board in accordance with Pharmacovigilance guidelines and in compliance with local regulations.

The Investigator is to notify the appropriate Institutional Review Board/Independent Ethics Committee IRB/IEC or other relevant ethical review board of SADRs occurring at the site and other AE reports received from Amgen, in accordance with local procedures and statutes.

The AE severity grading scale used will be the Amgen adverse event standard grading score. The severity grading scale used in this study is described in Appendix D.

Section: 10.2, Sample Size Considerations

Replace:

Table 1

With:

Table 2

Section: Appendix B, Sample Adverse Drug Reaction Report

Replace:

Existing form

With:

Updated form

Section: Appendix C, Pregnancy Notification Worksheet

Replace:

Existing form

With:

Pregnancy and Lactation Notification Worksheets