# Title: Prospective Observational Study to Describe Characteristics and Management of Patients With Postmenopausal Osteoporosis Treated With Prolia® in Routine Clinical Practice

**Amgen Protocol Number 20110132**

**AMG 162 - Prolia® (denosumab)**

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**Investigator's Agreement**

I have read the attached protocol entitled Prospective Observational Study to Describe Characteristics and Management of Patients With Postmenopausal Osteoporosis Treated With Prolia® in Routine Clinical Practice dated 28 February 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 (as applicable by local law).

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)

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## Protocol Synopsis

**Title:** Prospective Observational Study to Describe Characteristics and Management of Patients With Postmenopausal Osteoporosis Treated With Prolia® in Routine Clinical Practice

**Study Phase:** Observational

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

**Study Objective:**

The objective of this prospective, observational study in Czech Republic and Slovakia is to describe per country the characteristics of women treated with Prolia® (denosumab) in routine clinical practice and the clinical management of these patients during the first 2 years of treatment.

**Hypotheses:** The study is descriptive in nature, and a formal hypothesis will not be tested in this observational, single-arm study.

**Study Outcomes:**

- Occurrence (yes/no) of patient receiving all prescriptions and injections of Prolia® from the initial prescribing physician's office
- Occurrence (yes/no) of patient receiving an individual prescription and injection of Prolia® from the initial prescribing physician office by injection
- Occurrence (yes/no) of patient receiving all prescriptions and injections of Prolia®, whether or not the injections are given at the initial prescribing physician's office
- Occurrence (yes/no) of patient with a referral by the prescribing physician to other health care providers for continuation or follow up of care by type of physician
- Types of health care providers administering an individual injection of Prolia® inside or outside the initial prescribing office by each individual injection
- Number of Prolia® injections received by each patient during the follow-up period
- Occurrence (yes/no) of patient having radiologic bone assessments pre-treatment with Prolia®, and during the study
- Occurrence (yes/no) of patient having osteoporosis-related laboratory examinations pre-treatment with Prolia®, and during the study
- Incidence (yes/no) of patients with ADR to Prolia®
- Incidence (yes/no) of patients with serious ADR to Prolia®

**Study Design:**

This is a multi-center, international, non-interventional, prospective, observational study in PMO (postmenopausal osteoporosis) patients who received at least one injection of Prolia® 60 mg Q6M, SC (subcutaneous) in Czech Republic and Slovakia. This observational study will not alter the routine clinical management of patients and will comply with all applicable local regulations in the countries in which it is being conducted.

Prolia® naive patients will be eligible to enroll within 8 weeks after initiation of Prolia® treatment (ie 8 weeks after receiving the first injection). The decision to treat the patient with Prolia® must be made independent of and prior to their enrollment in the study. However, writing of the prescription for Prolia®, the first Prolia® injection and/or administration of informed consent (as applicable by local country laws and regulations) may happen at the same visit. It is expected that patients will receive their scheduled Prolia® injection every 6 months as part of their routine clinical care.

Approximately 300 patients will be enrolled in Czech Republic and 300 in Slovakia. The estimated duration of enrollment is approximately 12 months. No study drug will be administered as part of the study. The protocol will specify that investigators will offer participation in the study to all patients treated with Prolia® during the enrollment period until they reach their contracted number of patients. Detailed data obtained as part of routine clinical practice will be collected at the initial visit, either directly or from medical record, to characterize the patient population. It is anticipated that patients will return to the clinic every 6 months to receive their Prolia® prescription

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and/or injections. After the initial visit, information regarding Prolia® prescription and administration, procedures pertaining to osteoporosis and Prolia®, concomitant medication use, and non-serious and serious ADRs will be obtained during routine clinical visits and recorded for up to approximately 2 years after entering the study.

The study will describe the profile of patients treated with Prolia® and the clinical management of these patients during the first 2 years of treatment. Patient and site characteristics will be collected at baseline according to the following 4 dimensions:

- Socio-demographic related
- Condition-related (osteoporosis)
- Patient-related
- Physician-related (including geographic region, specialty)

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**Sample Size:** Approximately 300 patients in the Czech Republic and 300 in Slovakia.

**Summary of Patient Eligibility Criteria:**

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

- Women with a clinical diagnosis of PMO
- Decision has been made to treat patient with Prolia® 60 mg once every 6 months
- Have received their first injection of Prolia® within 8 weeks prior to enrolling in this study
- Appropriate written informed consent has been obtained (as required per local country regulations)

Patients meeting the following exclusion criteria are not eligible to participate in the observational study:

- Patients who are participating in ongoing or have participated in previous denosumab clinical trials
- Participation in other clinical or device trials in the last 6 months
- Contra-indicated for treatment with Prolia®
- Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent.

**Amgen Investigational Product Dosage and Administration:** None

**Non Amgen Investigational Product Dosage and Administration:** None

**Non Amgen Non-investigational Product Dosage and Administration:** None

**Control Group:** None

**Procedures:**

There are no procedures or changes to routine clinical management of PMO patients. It is anticipated that patients will return to the clinic every 6 months to receive their Prolia® prescription and/or injections. Patients will be followed for approximately 2 years after their initial visit. Clinical information obtained for routine clinical practice will be recorded where available, including Prolia® administration, previous and current therapies, medical history (including fracture), ADRs and serious ADRs and co-morbidities (Appendix A. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A (Information Obtained during Routine Clinical Practice).

**Statistical Considerations:**

This is an observational study for which the analysis will be descriptive in nature; no formal hypothesis will be tested. Frequency distributions will be described for categorical variables. Continuous variables will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values. All study outcomes and baseline characteristics will be summarized by country. For selected study

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outcome related to the clinical management of these patients, point estimate and 95% confidence interval will be provided as well by country. Summary of the study outcomes by country and selected baseline variables will be provided. Appropriate outcomes specific for a prescription/ injection will be summarized by prescription/injection (1st, 2nd, 3rd and 4th).

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

**Sponsor:** See Protocol Title Page

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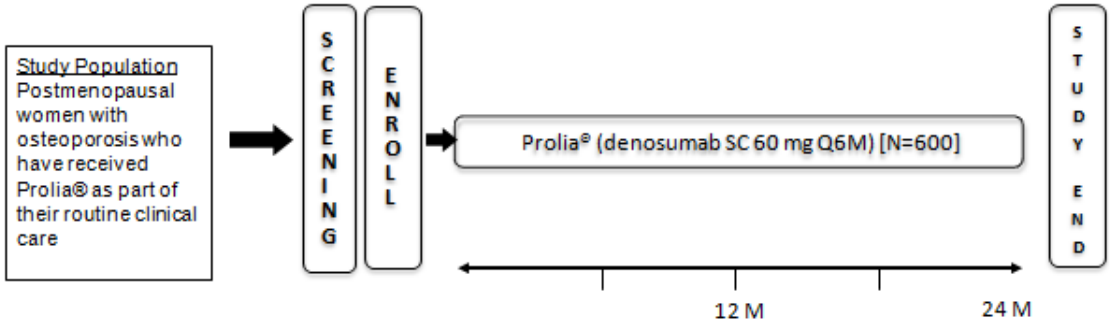
## Study Design and Treatment Schema

20110132: Prospective Observational Study to Describe Characteristics and Management of Patients With Postmenopausal Osteoporosis Treated With Prolia® in Routine Clinical Practice




The decision to treat the patient with Prolia® 60 mg Q6M SC should occur independent of and prior to their enrollment in the study

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## Study Glossary

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| BMD | Bone Mineral Density |
| BMI | Body Mass Index |
| BPs | Bisphosphonates |
| CI | Confidence Interval |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EU | European Union |
| HCP | Health Care Professional |
| IEC | Independent Ethics Committee |
| IVRS | Interactive Voice Response System |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OP | Osteoporosis |
| OPG | Osteoprotegerin |
| PMO | Postmenopausal Osteoporosis |
| Q6M | Once every 6 months |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| SC | Subcutaneous |

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## 1. OBJECTIVES

The objective of this prospective, observational study is to describe characteristics of postmenopausal women treated with Prolia® (denosumab) in routine clinical practice and to describe the clinical management of these patients during the first 2 years of treatment in Czech Republic and Slovakia.

## 2. BACKGROUND AND RATIONALE

### 2.1 Disease

Osteoporosis is a common, systemic skeletal disorder characterized by low bone mass and compromised bone strength predisposing individuals to an increased risk of fracture (NIH Consensus 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 (Cree et al, 2003). About 40 to 50% of women are at risk of having an osteoporotic fracture in their lifetimes (Dennison et al, 2006). In Europe, the number of osteoporotic fractures was estimated at 3.79 million/year of which 0.89 million were hip fractures (Kanis and Johnell, 2005).

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

Denosumab is a fully human monoclonal antibody that inhibits RANKL, an essential regulator of osteoclast differentiation, activation and survival. Administration of denosumab 60 mg SC (subcutaneous) every 6 months (Q6M) (Prolia®) has been shown to decrease bone remodeling with consequent increases in bone mineral density (BMD) and decreased risk for new vertebral, nonvertebral, and hip fractures (Cummings e al. 2009).

### 2.2 Prolia® Background

Prolia® (denosumab) is a fully human monoclonal antibody that inhibits RANKL, an essential regulator of osteoclast differentiation, activation and survival. It can bind and

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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 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 Iceland, Liechtenstein, Norway and Switzerland for the treatment of osteoporosis in postmenopausal women at increased risk of fracture

### 2.3 Rationale

After regulatory approval is granted for pharmaceutical products, many countries request data regarding patient demographics to ensure that each drug is being used in the population for which it was intended. Moreover for injectable drugs like Prolia®, countries seek information on the manner of administration to ensure proper use.

In Czech Republic, Prolia® was approved on 26 May 2010 and is the only injectable product available in retail pharmacies (all other injectables are hospital products). Prolia® also was approved in Slovakia on 26 May 2010. In both countries, Prolia® is prescribed predominantly by specialists and reimbursed for PMO patients with a T-score ≤ -2.5 or prior fracture and / or limited by other reimbursement restrictions, as applicable by local country regulations.

By collecting information on patient characteristics including demographics, comorbid conditions and use of concomitant medications, study findings will help describe women receiving Prolia® for osteoporosis in the Czech Republic and Slovakia. Special attention will be given to collecting data enabling description of factors determining therapeutic choice and the patient's fracture risk; comorbid conditions influencing bone health (including systemic, metabolic, rheumatic, thyroid, parathyroid, renal and lung); clinical factors related to osteoporosis (prior fracture, age, ambulatory status, bone turnover markers, BMD T-score, body mass index, Ca (calcium) and vitamin D intake); lifestyle factors (smoking, alcohol and drug use/abuse); socioeconomic status (employed, retired); and physician/healthcare professional related information. Data from this study will provide information about management practice patterns in patients for whom, in the opinion of the prescribing physician, Prolia® was deemed to be appropriate.

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### 2.4 Clinical Hypotheses

The study is descriptive and no formal hypothesis testing will be performed in this prospective, observational study. However demographic and clinical characteristics of postmenopausal patients who received at least one injection of Prolia® (denosumab 60 mg) will be described.

## 3. EXPERIMENTAL PLAN

### 3.1 Study Design

This is a multi-center, international, non-interventional, prospective, observational study in PMO patients who received at least one injection of Prolia® 60 mg Q6M, SC in Czech Republic and Slovakia. This observational study will not alter the routine clinical management of patients and will comply with all applicable local regulations in the countries in which it is being conducted.

Patients will be eligible to enroll within 8 weeks after receiving their first Prolia® injection. The decision to treat the patient with Prolia® must be made independent of and prior to their enrollment in the study. However, the writing of the prescription for Prolia®, the first Prolia® injection and/or administration of informed consent (as applicable by local country laws and regulations) may happen at the same visit. It is expected that patients will receive their scheduled Prolia® injection every 6 months as part of their routine clinical care.

Approximately 300 patients will be enrolled in Czech Republic and 300 in Slovakia. The estimated duration of enrollment is approximately 12 months. No study drug will be administered as part of the study. Investigators may offer participation in the study to all women treated with Prolia® during the enrollment period until they reach their contracted number of patients. Detailed data obtained as part of routine clinical practice will be collected at the initial visit, either directly or from medical record, to characterize the patient population. It is anticipated that patients will return to the clinic every 6 months to receive their Prolia® prescription and/or injections. After the initial visit, information regarding Prolia® prescription and administration, procedures pertaining to Prolia® administration and osteoporosis, concomitant medication use, and non-serious and serious ADRs will be obtained during routine clinical visits and recorded for up to approximately 2 years after entering the study.

The study will describe the profile of patients treated with Prolia® and the clinical management of these patients during the first 2 years of treatment. Patient and site

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characteristics will be collected at baseline according to the following 4 dimensions, when available:

- Socio-demographic related
- Condition-related (osteoporosis)
- Patient-related
- Physician-related (including geographic region, specialty)

In this observational study, ADRs and serious ADRs related to Prolia® will be collected and reported. ADRs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Additional information as outlined in Appendix B will be collected during routine clinical visits over a period of approximately 2 years. Given that the frequency of Prolia® administration is every 6 months, a 2-year observation period is thought appropriate to ascertain treatment practices and document ADRs and serious ADRs.

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

The study outcomes are defined in Section 10.1.

### 3.2 Number of Centers

The study will be conducted in approximately 30 representative (country specific) sites (15 each in Czech Republic and Slovakia). Additional sites may be added or removed as deemed necessary to ensure enrollment of the target number of patients. After feasibility assessment, sites selected will represent those providing 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.

### 3.3 Number of Patients

Participants in this clinical investigation shall be referred to as “patients”.

Approximately 600 patients (about 300 each in Czech Republic and Slovakia) 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. Patients providing appropriate written informed consent and fulfilling inclusion and exclusion criteria will be

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eligible to enroll in the observational study. Enrolled patients will have a follow-up period of approximately 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 24 months of observation or when the last patient ends her participation in the study.

## 4. PATIENT ELIGIBILITY

Postmenopausal women with OP who receive an injection of Prolia® and 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 entering the study, an appropriate written informed consent must be obtained as applicable by local country regulations (see Section 11.1).

### 4.1 Inclusion Criteria

4.1.1 Women with a clinical diagnosis of postmenopausal osteoporosis

4.1.2 Decision has been made to treat with Prolia® 60 mg once every 6 months

4.1.3 Have received their first injection of Prolia® within 8 weeks prior to enrolling in this study

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

### 4.2 Exclusion Criteria

4.2.1 Participating in ongoing or have participated in previous denosumab clinical trials

4.2.2 Participation in other clinical or device trials in the last 6 months

4.2.3 Contra-indicated for treatment with Prolia® according to the approved applicable local product label.

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

## 5. PATIENT 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.

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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 identification numbers will be assigned in sequential order within a site beginning with 132XXXXX001, 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 have recently (within 8 weeks) initiated treatment with Prolia® in routine clinical practice. No study-specific treatment will be provided and 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 unless patients discontinue the study or are lost to follow up. Information regarding the clinical management of the patients receiving Prolia® may be collected whenever available, even after treatment discontinuation.

There are no procedures or changes to routine clinical management of patients. It is anticipated that patients will return to the clinic every 6 months to receive their Prolia® prescription and/or injections. Patients will be followed for approximately 2 years after their initial visit. Available clinical information obtained for routine clinical practice (including those already recorded on the patient medical records ie, baseline characteristics) will be recorded, including Prolia® administration, previous and current therapies, medical history (including fracture history), ADRs and serious ADRs and co-morbidities (Appendix A).

### 6.1 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate routine clinical care including calcium and vitamin D supplementation.

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## 7. STUDY PROCEDURES

There are no procedures or changes to routine clinical management of patients. It is anticipated that patients will return to the clinic every 6 months to receive their Prolia® prescription and/or injections. Patients will be followed for approximately 2 years after their initial visit. Available clinical information obtained for routine clinical practice (including those already recorded on the patient medical records for baseline characteristics) will be recorded, including Prolia® administration, previous and current therapies, medical history (including fracture), ADRs and serious ADRs and co - morbidities (Appendix A).

Patients who switch to another therapy or discontinue treatment will not be followed up for more than 6 months after their last Prolia® injection.

## 8. REMOVAL AND REPLACEMENT OF PATIENTS

### 8.1 Removal of Patients

Patients have the right to withdraw fully 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 Patients

Participants 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.

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## 9.1 Adverse Drug Reaction

### 9.1.1 Definition of Adverse Drug Reaction

An Adverse Drug Reaction (ADR) is defined as an adverse event associated with a given medication at normal dosage.

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.

### 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 injection of Prolia® through the end of study are captured. Moreover, these events will also be captured using the applicable eCRF (electronic Case Report Form) (eg, Adverse Drug Reaction 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 record the ADR and assign the following ADR attributes:

- ADR diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Date(s) of onset and resolution,
- Severity, 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 Drug Reaction

### 9.2.1 Definition of Serious Adverse Drug Reaction

A SADR is a SAE (serious adverse event) that is considered related to the medicinal product.

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A serious adverse event 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.

### 9.2.2 Reporting Procedures for Serious Adverse Drug Reaction

The investigator is responsible for ensuring that all SADRs related to Prolia® from the first injection 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/faxed to Amgen within 1 working day of discovery or notification of the event to the designated safety fax number – 800 900 625 for Czech Republic, 0800 044 033 for Slovakia.

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 Drug Reaction Summary eCRF).

Amgen will report SADRs as required to regulatory authorities, in compliance with all reporting requirements according to local regulations for observational studies.

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### 9.3 Pregnancy Reporting

Any confirmed pregnancy 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 D). Women who become pregnant during Prolia® treatment are encouraged to enrol in Amgen's Pregnancy Surveillance program. Follow-up information on the pregnancy outcome should be communicated by the investigator to Amgen Global Safety as soon as available.

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Study Outcomes, Subsets, and Covariates

#### 10.1.1 Study Outcomes

The following outcomes are to characterize the clinical management of the patients during the first 2 years of treatment with Prolia®:

- Occurrence (yes/no) of patient receiving all prescriptions and injections of Prolia® from the initial prescribing physician's office
- Occurrence (yes/no) of patient receiving an individual prescription and injection of Prolia® from the initial prescribing physician office by each individual injection
- Occurrence (yes/no) of patient receiving all prescriptions and injections of Prolia®, whether or not the injections are given at the initial prescribing physician's office
- Occurrence (yes/no) of patient with a referral by the prescribing physician to other health care providers for continuation or follow up of care by type of physician
- Types of health care providers administering an individual injection of Prolia® inside or outside the initial prescribing office by injection
- Number of Prolia® injections received by each patient during the follow-up period
- Occurrence (yes/no) of patient having radiologic bone assessments pre-treatment with Prolia®, and during the study
- Occurrence (yes/no) of patient having osteoporosis related laboratory examinations pre-treatment with Prolia®, and during the study.

The following outcomes are to characterize the safety of patients during the first 2 years of treatment with Prolia®:

- Incidence (yes/no) of patients with ADR to Prolia®.
- Incidence (yes/no) of patients with serious ADR to Prolia®.

PMO patients treated with Prolia® will be characterized according to the 4 dimensions of patient and site characteristics when available, as specified in Section 10.1.3

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### 10.1.2 Analysis Set

The Full Analysis Set will consist of all enrolled patients satisfying the inclusion/exclusion criteria that receive at least one Prolia® injection and have a non-missing enrollment date. All analyses will be performed on this analysis set.

### 10.1.3 Subsets and/or Covariates

The following 4 dimensions of variables will be collected at baseline, either directly as part of routine clinical practice, or from medical records when available:

**Socio-demographic related**

- Educational level (no formal education, elementary education, secondary education, university)
- Patient living situation (at home with spouse/family, at home with care/support, at home alone, nursing home)
- Patient employment status (unemployed, retired, employed, self employed)
- Country: Czech Republic or Slovakia

**Condition-related (osteoporosis)**

- Body mass index (≤ 25 or > 25 kg/m$^2$)
- Age at menopause (years)
- Cause of menopause (natural onset, clinically/surgically induced)
- Height loss since maximal height (yes, no)
- Height loss in centimeters (cm)
- Previous fracture (yes, no)
  - Previous hip fracture (yes, no)
  - Previous vertebral fracture (yes, no)
  - Other previous fractures (yes, no)
- Time since the most recent previous fracture to first injection (< 12 months or ≥ 12 months)
- Previous hospitalization for osteoporotic fracture and/or surgical osteoporotic fracture treatment (yes, no)
- One or more falls experienced during the past 12 months (yes, no)
- One or more episodes of immobility experienced during the past 12 months (yes, no)
- Parent fractured hip (yes, no)
- Current smoker (yes, no)
- Former smoker (yes, no)
- Systemic glucocorticoid use (yes, no)
- Secondary osteoporosis (yes, no)
- Alcohol 3 or more units per day (yes, no)

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- Femoral neck BMD T-score
- Lumbar spine BMD T-score
- Total hip BMD T-score

**Patient-related:**

- Age (years)
- Age group (< 65, ≥ 65 to <75, ≥ 75 years)
- Time since PMO diagnosis
- Number of prescription medications taken at baseline
- Number of comorbidities
- Any chronic medical condition (yes, no)
- Type of chronic medical condition (diabetes/osteoporosis/hypertension/other)
- Ever exposed to prior PMO therapy (yes, no)
- Exposed to prior PMO therapy during the 12 months prior to enrollment (yes, no)
- Calcium and/or Vitamin D supplementation at baseline (yes, no)
- History of discontinuation of prescription osteoporosis therapy (yes, no)

**Physician-related:**

- Type of prescribing HCP (Physician specialty: Orthopedist, Traumatologist, Rheumatologist, Internist, Endocrinologist, Gynecologist)
- Physician years of practice (1 to 4, 5 to 9, ≥ 10)
- Physician practice reminder (yes, no)
- Type of reminder
- Centre hospital or non-hospital based (hospital, non-hospital)
- Centre academic or non-academic (academic, non-academic)
- Reason for prescribing Prolia® (low BMD T-score, history of osteoporotic fracture, multiple risk factors for fracture, failed other available osteoporosis therapy, intolerant to other osteoporosis therapy, other)
- Size of the clinic (small [≤ 2 doctors], medium [between 3 and 5 doctors] or large [≥ 6 doctors])
- Sole physician or group of them
- Geographic region (rural, urban)

### 10.2 Sample Size Considerations

This is an observational study for which the analysis will be descriptive in nature.

Country commitments require that patients and management of patients receiving Prolia® be characterized and described, and safety (Prolia® -related ADRs and serious ADRs as defined in Section 9.1.1) be reported.

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To characterize this Prolia® population, a sample size of approximately 300 patients per country is proposed. For Slovakia and Czech Republic, a sample of the population will be selected from the different regions (districts). There are 17 regions in Czech Republic and 8 regions in Slovakia, and an attempt will be made to recruit sites from as many different regions as possible. For Czech Republic, about 15 sites distributed around the 17 regions will enroll approximately 20 patients per site to provide about 300 patients. In Slovakia, approximately 15 sites distributed around the 8 regions will enroll approximately 20 patients per site or about 300 patients total.

**Rationale for the country sample size**

The sample size of approximately 300 patients per country is proposed based on the chances of capturing any patient-related characteristics that has a prevalence of approximately 1% or more in the population. As shown in the table below, the chances of observing at least one event with a prevalence rate of 1% or more is equal to or greater than 90% when the sample size is at least 250.

**Table 1. Probability of Detecting at Least One Event by Size of Group and Prevalent Rate**

| True prevalent rate (p) | Group size (N) | | | | | |
|---|---|---|---|---|---|---|
| | 15 | 20 | 100 | 200 | 250 | 300 |
| 0.01% | < 0.01 | < 0.01 | 0.01 | 0.02 | 0.02 | 0.03 |
| 0.5% | 0.07 | 0.10 | 0.39 | 0.63 | 0.71 | 0.78 |
| 1% | 0.14 | 0.18 | 0.63 | 0.87 | 0.92 | 0.95 |
| 5% | 0.54 | 0.64 | 0.99 | > 0.99 | > 0.99 | > 0.99 |
| 6% | 0.60 | 0.71 | > 0.99 | > 0.99 | > 0.99 | > 0.99 |
| 8% | 0.71 | 0.81 | > 0.99 | > 0.99 | > 0.99 | > 0.99 |
| 10% | 0.79 | 0.88 | > 0.99 | > 0.99 | > 0.99 | > 0.99 |
| 15% | 0.91 | 0.96 | > 0.99 | > 0.99 | > 0.99 | > 0.99 |

Note: The probability of detecting at least one event was calculated by assuming that the number of events has a binomial distribution with parameters (N, p).

Moreover, 95% CI may be provided around selected percentage point estimates, and a sample size of approximately 300 patients is suggested based on the precision of these estimates. The sample size of approximately 300 patients per country will provide a maximum half width (based on an estimate of prevalent rate of 50%) for the 95% CIs around the percentage point estimates of approximately 6%, as shown below.

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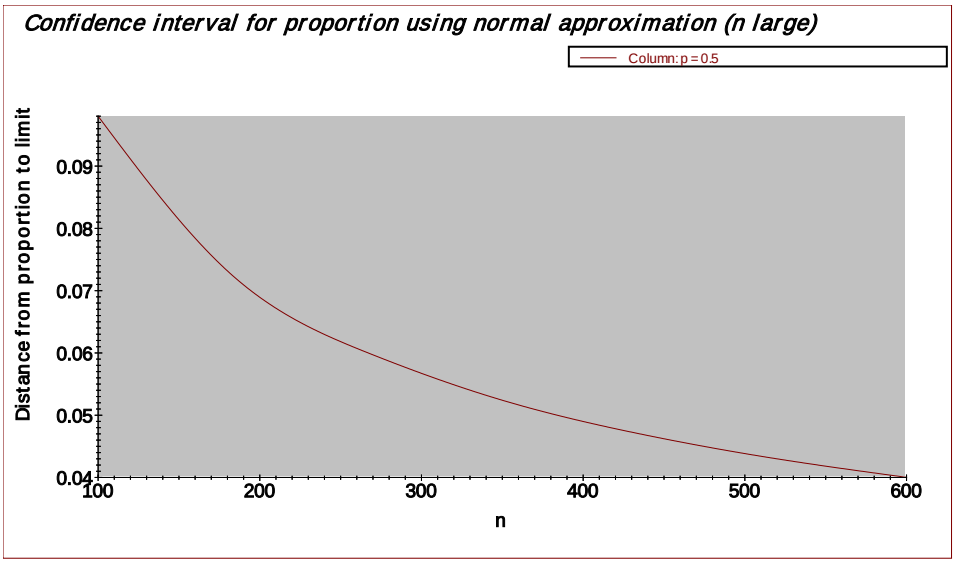
**Figure 1. Half-width of the 95% Confidence Interval – Country Sample Size**




### 10.3 Interim Analysis and Early Stopping Guidelines

An interim analysis is planned to be performed in each country to describe patient characteristics and provide information on the clinical management of PMO patients. This analysis will include data up to 12 months after the initial administration of Prolia® in all participants.

The design of the study will not be changed based on the interim analysis results. No stopping rules will be applied due to the observational nature of this study.

### 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 no formal hypothesis will be tested.

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

#### 10.4.2 Analysis of Key Study Outcomes

##### 10.4.2.1 Outcomes

All study outcomes and baseline characteristics will be summarized by country. For selected study outcome related to the clinical management of these patients, point estimate and 95% confidence intervals will be provided as well by country.

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Summary of the study outcomes by country and selected baseline variables also will be provided.

Appropriate outcomes, specific for a prescription/ injection will be summarized by country and prescription/injection (1st, 2nd, 3rd and 4th).

#### 10.4.2.2 Safety Outcomes

All ADRs and serious ADRs to Prolia® will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Patient incidence of ADRs and serious ADRs will be tabulated by system organ class and preferred term. Moreover, ADRs and serious ADRs leading to study discontinuation, discontinuation of Prolia® or associated with a fatal outcome will be tabulated by system organ class and preferred term.

## 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 section is applicable per local governing law and/or 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.

A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.

The investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/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

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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 his/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

Where applicable per local governing law and/or regulations 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 participants 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.

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

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### 11.3 Patient Confidentiality

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

- On the CRFs or other documents submitted to Amgen patients should be identified by a patient identification number only, with a complete and accurate date of birth on the demographics eCRF.
- For Serious Adverse Drug Reaction Events reported to Amgen, patients should be identified by their initials, date of birth, and a patient identification number.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

Where applicable per local governing law and/or regulations, 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.

### 11.4 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible patients

## 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 12.1 Protocol Amendments and Study Termination

Where applicable per local governing law and/or regulations 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

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

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

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, including the most recent date of Prolia® administration 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 where applicable per local governing law and/or regulations. 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 CRFs 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.

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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 where applicable per local governing law and/or regulations.

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 (as applicable by local law) and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (as applicable by local law), 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 (as applicable by local law). 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 principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

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

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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

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

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.

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## 13. REFERENCES

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NIH Consensus Development Panel on Osteoporosis Prevention, Diagnostics and Therapy. *Journal of the American Medical Association,* 2001. 285(6): 785-795

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Sambrook P, Cooper C. Osteoporosis. *Lancet.* 2006;367:2010-2018.

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# 14. APPENDICES

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## Appendix A. Information Obtained During Routine Clinical Practice

(To be recorded as available and if allowed per local country regulations)

| Data (as available and or applicable) | Enrollment | Follow up data | End of Study (24 months) or Early Termination |
|---|---|---|---|
| Informed consent | X | | |
| Type of prescribing health care professional | X | X | |
| Patient socio-demographics | X | | |
| Menopause history | X | | |
| Postmenopausal osteoporosis and fracture history | X | X | X |
| Previous osteoporosis medication | X | | |
| Medical history | X | | |
| Clinical risk factors | X | X | X |
| Behavioral risk factors | X | X | X |
| Calcium and Vitamin D supplementation | X | X | X |
| Current medication use | X | X | X |
| Prolia® administration[1] | X | X | X |
| Management practice of patient | | X | X |
| Adverse drug reaction (collection) | X | X | X |
| Discontinuation and reasons for discontinuation from Prolia® | | X | X |
| End of study/Early termination date | | | X |

[1]Part of routine clinical care of the patient.

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## Appendix B. Additional Safety Assessment Information

Adverse Event Severity 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 |

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## Appendix C. Sample Serious Adverse Drug Reaction Report Form

| AMGEN 20110132 | Serious Adverse Drug Reaction Report<br>*Notify Amgen Within One Working Day*<br>SELECT OR TYPE IN A FAX# | ☐New<br>☐Follow-up |
|---|---|---|

**1. SITE INFORMATION**

| File 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 | Race |
|---|---|---|---|---|
| | | | ☐F ☐M | |

**3. SERIOUS ADVERSE DRUG REACTION**

| Serious Adverse Drug Reaction: Diagnosis or Syndrome<br>If diagnosis is unknown, enter Signs / Symptoms<br>When Final Diagnosis is known, enter as Adverse Drug Reaction<br><br>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<br>Day Month Year | Date Ended<br>Day Month Year | Event Status Date code<br>(see codes below) | Reasonable possibility that the event may have been caused by Amgen drug?<br>(see codes below)<br>No ✓ | <br>Yes ✓ | Outcome of Event:<br>01 Resolved<br>02 Resolving<br>03 Not resolved<br>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<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|---|
| Was subject/patient hospitalized? ☐No ☐Yes, If yes, provide date(s) → | | |

**5. SUSPECT AMGEN PRODUCT**

| | Initial Start Date<br>Day Month Year | Prior to, or at time of Event:<br>Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product:<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld |
|---|---|---|---|---|---|---|
| Amgen Product: Prolia<br>Lot#: | | | | | | |
| Amgen Product: Prolia<br>Lot#: | | | | | | |
| Amgen Product:<br>Lot#: | | | | | | |
| Amgen Product:<br>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 ✓) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
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| | | | | | | | | | | | |



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| AMGEN 20110132 | Serious Adverse Drug Reaction Report<br>*Notify Amgen Within One Working Day* | ☐New<br>☐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: | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Units: | | | | | | | | | | | |
| | | | | | | | | | | | | |
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| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**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 events listed in section 3)*
*For each event in section 3, where relationship=Yes, please provide rationale.*

| Signature of Investigator or Designee | Title | Date |
|---|---|---|
| | | |



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## Appendix D. Pregnancy Notification Worksheet

| AMGEN<br>Study No.: | Site No. | Subject ID No. |
|---|---|---|

# PREGNANCY NOTIFICATION WORKSHEET

Did subject withdraw from the study? ₀❑ No ₁❑ Yes

| Sex ① | ①SEX CODES:<br>1 Female subject<br>0 Male subject partner |
|---|---|
| | |

| Estimated Date of Conception | | |
|---|---|---|
| Day | Month | Year |
| | | |

| Investigational Product Administration Start Date | | | Investigational Product Administration Stop Date | | |
|---|---|---|---|---|---|
| Day | Month | Year | Day | Month | Year |
| | | | | | |

| Fax to: | | |
|---|---|---|
| | | |
| Date Faxed | | |
| Day | Month | Year |
| | | |

*The investigator will be contacted for further information.*

**Please provide the following information:**

| Investigator Name: | Telephone:<br>( ) |
|---|---|
| Institution: | Site No.: |
| Address: | |

Form Completed By: _____ Date: _____

v4 14Apr04ab

Approved

ÚRAD KOŠICKÉHO SAMOSPRÁVNEHO KRAJA

Námestie Maratónu mieru 1, 042 66 Košice

**Amgen Slovakia s.r.o.**
MUDr. Alica Halgašová
Radlinskeho ul. 40 a
921 01 Piešťany

| Váš list číslo/zo dňa | Naše číslo | Vybavuje/linka | Košice |
|---|---|---|---|
| | 2671/2012-RU20/13460 | PhDr. Dringuš / 726 82 95 | 27.4. 2012 |

Vec: Rozhodnutie Etickej komisie Košického samosprávneho kraja - zaslanie

Etickej komisii Košického samosprávneho kraja bola doručená Vaša žiadosť o schválenie neintervenčného skúšania, protokol č.: **20110132**

***„Prospektívna pozorovacia štúdia na popísanie charakteristík a manažmentu pacientiek s postmenopauzálnou osteoporózou liečených prípravkom Prolia® v bežnej klinickej praxi.“***

*„Prospective Observational Study to Describe Charakteristics and management of Patients Treated With Prolia® in Routine Medical Practice.“*

Dňa 17.04.2012 sa uskutočnilo zasadnutie Etickej komisie Košického samosprávneho kraja, na ktorom bola prejednaná a schválená Vaša žiadosť.

V prílohe listu Vám týmto zasielame Rozhodnutie Etickej komisie Košického samosprávneho kraja.

S pozdravom

[redacted]

MUDr. Mária Grüllingová
predsedníčka Etickej komisie KSK

Prílohy: Rozhodnutie Etickej komisie KSK
Prezenčná listina

Etická komisia Košického samosprávneho kraja
Námestie Maratónu mieru 1
042 66 Košice, Slovakia
Tel: +421 55 726 8295
fax: 055/7268149

## STANOVISKO / STATEMENT

**ETICKÁ KOMISIA / ETHICS COMMITTEE**
**Názov Etickej komisie** / Name of Ethics Committee: Etická komisia Košického samosprávneho kraja
**Adresa Etickej komisie** / Ethics Committee address: Námestie Maratónu mieru 1, 042 66 Košice, Slovakia

**Pre** / To:
AMGEN GmbH
Head Office for Central & Eastern Europe
Franz Josefs Kai 47
A-1010 Vienna
Rakúsko

**Vec: Schválenie neintervenčného skúšania (protokol č. 20110132)**

**Názov štúdie** / Title of Study:

**Prospektívna pozorovacia štúdia na popísanie charakteristík a manažmentu pacientiek s postmenopauzálnou osteoporózou liečených prípravkom Prolia® v bežnej klinickej praxi.**

Prospective Observational Study to Describe Charakteristics and management of Patients Treated With Prolia® in Routine Medical Practice.

**Číslo protokolu** / No. Of protocol: **20110132**

**Zadavateľ** / Sponsor: **AMGEN GmbH, Head Office for Central & Eastern Europe, Franz Josefs Kai 47, A- 1010 Vienna**

**Predložené dokumenty** / ***Submitted documents***:

| **Documents** / dokumenty<br>**Version/Date** /verzia/dátum |
|---|

Etická komisia Košického samosprávneho kraja
Námestie Maratónu mieru 1
042 66 Košice, Slovakia
Tel: +421 55 726 8295
fax: 055/7268149

## STANOVISKO / STATEMENT

- Protokol 20110132, zo dňa 28. Februára 2012 / Protocol 20110132, 28 Feb 2012
- Formulár k informovanému súhlasu pacienta / Informed Consent form:
  SK 1.0 Hlavný informovaný súhlas_lokálna verzia v slovenčine_zo dňa 28. Februára 2012 / SK 1.0_Main Informed Consent_Local Slovak version_dated 28 February 2012
  SK 1.0 Hlavný informovaný súhlas_anglická verzia_zo dňa 28. Februára 2012 / SK 1.0_Main Informed Consent_English version_dated 28 February 2012
- Zoznam zúčastnených hlavných skúšajúcich 6.apríl 2012 / List of participating Principal Investigators 6th April 2012
- Životopisy zúčastnených hlavných skúšajúcich / CVs of participating Principal Investigators

**Vyššie predložené dokumenty boli dňa:** **17.4.2012**
The above submitted documents has been:

**Schválené:** ☒
Approved:

**Neschválené:** ☐
Not approved:

**Prehlasujem, že táto nezávislá etická komisia pracuje podľa požiadaviek ICH GCP a príslušných právnych noriem (vrátane zákona č. 576/2004 Z.z. v znení neskorších predpisov a zákona č. 362/2011 Z.z. v znení neskorších predpisov) a nariadení.**

"I hereby confirm that this Independent Ethics Committee is organized and operates according to ICH GCP requests and the applicable laws (including Act. No 576/2004 in the wording of later regulations and Act. No 362/2011 in the wording of later regulations) and regulations."

**Zoznam členov Etickej komisie je priložený.**
List of members of Ethics Committee is attached.

Košice
**Miesto**
Place

17.4.2012
**Dátum**
Date

[redacted]

MUDr. Mária Grüllingová

.....

**Meno, podpis a pečiatka predsedu EK**
Name, signature and stamp of the Chairman of the EC

KOŠICKÝ SAMOSPRÁVNY KRAJ

ETICKÁ KOMISIA Košického samosprávneho kraja
Námestie Maratónu mieru 1
042 66 Košice

# PREZENČNÁ LISTINA

Zasadnutie Etickej komisie KSK dňa **17.04.2012** o 14,00 hod., Zasadacia miestnosť č.209, Úradu KSK

| P.č. | Meno a priezvisko | funkcia | povolanie | organizácia | podpis | hlasovanie |
|---|---|---|---|---|---|---|
| 1. | MUDr. Mária Grüllingová | predsedníčka | internista / hematológ | Železničné zdravotníctvo Košice, s.r.o., Masarykova 9, 040 01 Košice | [redacted] | Áno / Nie |
| 2. | JUDr. Gabriela Ballaschová | člen | právnik | Detská fakultná nemocnica Košice, Trieda SNP č. 1, 040 01 Košice | [redacted] | Áno / Nie |
| 3. | MUDr. Peter Fedorčuk | člen | psychiater | Denné centrum duševného zdravia, Spišské nám. č. 1, 040 12 Košice | [redacted] | Áno / Nie |
| 4. | MUDr. Róbert Tóth, PhD. | člen | onkológ | Východoslovenský onkologický ústav, a.s., Rastislavova 46, 041 91 Košice | [redacted] | Áno / Nie |
| 5. | PharmDr. Marek Šarišský | člen | farmakológ | Lekárska fakulta UPJŠ, Ústav farmakológie, Trieda SNP č. 1, 040 11 Košice | [redacted] | Áno / Nie |
| 6. | MUDr. Štefan Lipčák | podpredseda | internista | Košický samosprávny kraj, lekár samosprávneho kraja, Nám. Maratónu mieru 1, 042 66 Košice | [redacted] | Áno / Nie |
| 7. | MUDr. Nataša Regendová | člen | internista / klinický farmakológ | Úrad pre dohľad nad zdravotnou starostlivosťou, Floriánska 19, 043 74 Košice | [redacted] | Áno / Nie |
| 8. | MUDr. Viera Karasová | člen | všeobecný lekár pre dospelých | Neštátne zdravotnícke zariadenie, Spišské nám. č. 1, 040 12 Košice | [redacted] | Áno / Nie |
| 9. | MUDr. Martina Kudláčová | člen | neurológ | Neštátne zdravotnícke zariadenie Goldmed, s.r.o., Rastislavova 45, 040 11 Košice | [redacted] | Áno / Nie |

PhDr. Peter Dringuš [redacted]
tajomník EK KSK

DÔVERA+
ZDRAVOTNÁ POISŤOVŇA

AMGEN Slovakia, s.r.o.
Radlinského 40a
92101 Piešťany

| Naša značka: | Vybavuje: | V Bratislave dňa: |
|---|---|---|
| 5249/1-12 -142 | Mgr. Barátová Lenka<br>02/57264179 | 30.5.2012 |

**Vec: Žiadosť o stanovisko k neintervenčnej klinickej štúdii – odpoveď**

Obchodná spoločnosť DÔVERA zdravotná poisťovňa, a. s. na základe ustanovenia § 45 zákona č. 362/2011 Z. z. o liekoch a zdravotníckych pomôckach a o zmene a doplnení niektorých zákonov udeľuje

**súhlas**

s priebehom neintervenčnej klinickej štúdie lieku Prolia ( Protokol číslo: 20110132), do ktorej sú zaradení poistenci obchodnej spoločnosti DÔVERA zdravotná poisťovňa, a. s.

Dôvod:

Neintervenčná klinická štúdia spĺňa kritérium podľa § 45 zákona č. 362/2011 Z. z. o liekoch a zdravotníckych pomôckach a o zmene a doplnení niektorých zákonov pre udelenie súhlasu zdravotnou poisťovňou.

[redacted]

PharmDr. Alžbeta Arvaiová
Riaditeľka úseku zdravotných činností

[redacted]