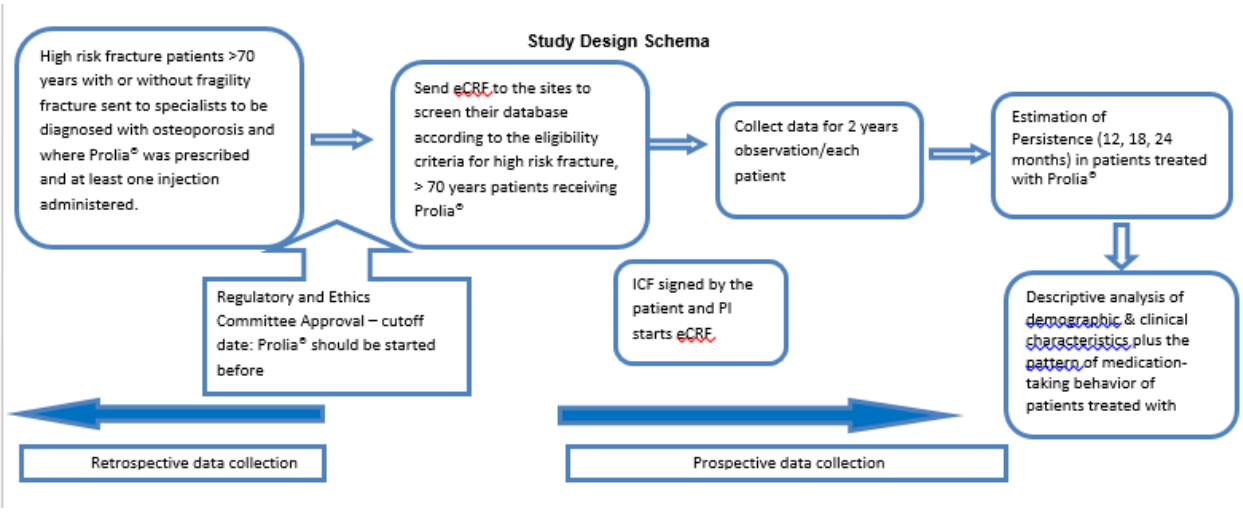
Product: Prolia
Protocol Number: 20160302
Date: 19.01.2017

Study Title: Prolia® persistence in post-menopausal women with osteoporosis, over 70 years, at increased risk of fracture, treated in routine clinical practice in Bulgaria

Research Question and Objectives: The purpose of this study is to estimate persistence with Prolia® in Prolia® treated at increased risk of fracture postmenopausal women, aged >70 years, at 12, 18 and 24 months in real life clinical practice in Bulgaria.
Objective is to estimate the proportion of patient at increased risk of fracture on Prolia® treatment for 2 years.
Demographic and clinical characteristics in -increased risk of fracture women >70 years with osteoporosis and treated with Prolia® will be described.



Primary Objective(s)

To estimate persistence with Prolia® in Prolia treated post-menopausal women with osteoporosis, aged >70 years, at increased risk of fracture, at 12, 18 and 24 months in real life clinical practice in Bulgaria.

Secondary Objectives(s)

- To describe demographic and clinical characteristics at increased risk of fracture women >70 years with osteoporosis and treated with Prolia.

- To describe the pattern of medication-taking behaviour up to 12 and 24 months in increased risk of fracture women > 70 years with osteoporosis and treated with Prolia®
- To describe bone mineral density (BMD) changes and safety in increased risk of fracture patients with osteoporosis over 70 years and treated with Prolia®.

No formal hypothesis will be tested in this observational study. The study will be descriptive in nature and provide an estimation of persistence with Prolia® at 12, 18 and 24 months in post-menopausal women with increased risk of fracture with osteoporosis, aged over 70 years in Bulgaria. Estimates along with 95% confidence intervals will be provided.

Consistent with the greater BMD increases observed in interventional and observational clinical trials, the low discontinuation rate and high persistence among women at increased risk of fracture receiving Prolia® could lead to improved clinical outcomes, including fracture risk reduction.

Study Design:

This is a national retrospective and prospective observational study based on clinical data of PMO women at increased risk of fracture receiving treatment with Prolia® for osteoporosis in routine clinical practice in Bulgaria. Eligibility for enrolment and baseline data including demographics and a patient's baseline (pre-enrolment) Prolia® injection will be collected retrospectively from medical records. Eligible patients will be considered enrolled in the prospective part of the protocol once they have signed the informed consent form (ICF) and will be followed for 24 months from first Prolia® pre-enrolment injection.

Study Population and Data Source:

Approximately 250 postmenopausal women > 70 years at increased risk of fracture, with/without previous fracture in real life clinical practice referred by orthopedic, neurology or other clinical outpatients and hospital settings to endocrinology and rheumatology centers to be diagnosed with osteoporosis and treated with Prolia® as per specialist's decision will be included in the study.

Inclusion criteria:

- Women with osteoporosis >70 years old, referred to endocrinologists or rheumatologists by orthopedic, neurology or other clinics/outpatient practices – to be diagnosed with Dual energy X-ray absorptiometry (DXA) and treated with Prolia®.

- The patient - meeting FRAX criteria for high risk: either ≥ 3% risk for hip fracture or ≥20% for major osteoporotic fracture
- The patient has received at least 1 Prolia® injection prior to approval of the study by Bulgarian Regulatory Agency and Bulgarian Central Ethics Commission. The date of the approval comes into force when Amgen has been handed the written decisions.

Exclusion criteria**:**

- Participation in clinical or device trials in the last 6 months
- Patient is currently participating or has participated in Prolia® clinical trials
- Patient is on other anti-osteoporosis medication at the time of enrolment (e.g. oral/i.v. bisphosphonates, or anabolics). Vitamin D and Calcium supplementation are not considered as osteoporosis medication and therefore are permitted.

Primary objective

To estimate persistence with Prolia® in Prolia® treated post-menopausal women with osteoporosis, aged >70 years, at increased risk of fracture, at 12, 18 and 24 months in real life clinical practice in Bulgaria.

Secondary objectives

- To describe demographic and clinical characteristics in increased risk of fracture women >70 years with osteoporosis and treated with Prolia®.
- To describe the pattern of medication-taking behaviour up to 12 and 24 months in increased risk of fracture women > 70 years with osteoporosis and treated with Prolia®
- To describe BMD changes and safety in increased risk of fracture women > 70 years with osteoporosis and treated with Prolia®

Primary Outcome Measure:

Persistence to Prolia®, time to non-persistence/discontinuation

Secondary Outcomes:

- Age, age at menopause, prior fragility fracture, prior PMO therapy, history of treatment discontinuation of osteoporosis therapy, reasons for discontinuation, secondary

osteoporosis: yes /no, systemic glucocorticoids: yes /no, comorbidities, previous hospitalizations, concomitant medications, FRAX at baseline, smoking, alcohol intake.

- Number of injections received per patient at the end of the study and number/percentage of patients treated with Prolia® after 12, 18 and 24 months of treatment initiation reason for discontinuation.
- Changes from baseline in BMD T-score, percentage of patients who achieved BMD T-score >-2.5, patient incidence of fractures, patient incidence if adverse drug reactions (ADRs)

Data Analysis

Baseline characteristics will be summarized using descriptive statistics. Counts and percentages will be provided 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.

Persistence will be measured as the time from initiating Prolia® to discontinuation at 12, 18 and 24 months and will be estimated as the proportion of patients receiving their injections by the specialist filling within the permissible gap in therapy. Patients not within the permissible gap will be considered as non-persistent.

Persistence is dependent on how the permissible gap is defined. In the primary analysis, the permissible gap will be set to 60 days. Sensitivity analyses will be carried out for the measurement of persistence by changing the permissible gap from the 60-day baseline analysis to 30 and 90 days.

Study period:

The study includes patients who have received at least 1 injection of Prolia® prior to study approval by Bulgarian Regulatory Agency and Central Ethics Commission. The date when the documents have been received by Amgen Bulgaria will be considered a cutoff date – after which no patients initiating Prolia® will be allowed to be included. The enrolment period will consist of a 6 months retrospective period and prospective 3 months period after the site is open in order for PI to have enough time to upload all suitable patients found in the database. Observation period will be 24 months for each patient individually from first pre-enrolment Prolia® injection. The

startup day (enrolment date) when the patient enrolls in the study will be the day when ICF is signed.