1. ABSTRACT

- **Title**

The Safety and Effectiveness of Denosumab Among Chinese With Osteoporosis and Glucocorticoid Exposure – a Real World Study in Taiwan

- **Keywords**

Real-world evidence, Prolia, clinical fracture, glucocorticoid-induced osteoporosis, osteonecrosis of the jaw

- **Rationale and Background**

The efficacy and safety of Prolia® (denosumab) in glucocorticoid-induced osteoporosis (GIOP) was demonstrated in a multicenter, 24-month, double-blind, active-controlled clinical trial of 795 subjects receiving glucocorticoids randomly assigned (1:1) to either 60 mg subcutaneous Prolia every 6 months or 5 mg oral risedronate daily (Saag et al, 2019). Supported by this clinical trial, Prolia was first approved for treatment of GIOP in men and women at high risk for fracture in May 2018 in the United States, and subsequently approved in June 2018 in the European Union for treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients with increased risk of fracture. Within regions of Chinese populations, Prolia was approved for GIOP in April 2019 in Taiwan and March 2021 in Hong Kong. The GIOP indication for Prolia in Taiwan states, "treatment of glucocorticoid-induced osteoporosis."

This study was conducted to further inform the benefit-risk profile of Prolia among Chinese adults with osteoporosis and glucocorticoid exposure. Context for results of the study was provided by the totality of evidence from prior clinical and real-world studies.

- **Research Question and Objectives**

Among Chinese patients with osteoporosis and glucocorticoid exposure, and treated with Prolia in clinical practice the objectives were:

Primary Objectives

- Evaluate the effectiveness of Prolia for the reduction of clinical fractures
- Characterize the safety of Prolia

Exploratory Objectives

- Describe percentage change from baseline to first measured BMD during Prolia treatment

- **Study Design**

This retrospective cohort study provided the incidence rates of effectiveness and safety endpoints among glucocorticoid-treated patients with osteoporosis. The incidence rates of effectiveness endpoints, including the primary endpoint (hip fracture) and secondary endpoints (clinical vertebral and nonvertebral fractures), were compared between an on-treatment cohort (patients who received 2 or more doses of Prolia 60 mg subcutaneously every 6 months) versus an off-treatment cohort (patients who discontinued after 1 dose of Prolia). The off-treatment cohort was selected to limit the bias related to the initial treatment decision by the physician and to leverage the context that a single dose of Prolia has no known benefit for reducing fracture risk, thereby the off-treatment cohort approximated the placebo arm of a clinical trial. The incidence rates of safety endpoints, including 3 important identified risks in the Core Risk Management Plan for Prolia, were characterized among all glucocorticoid-treated patients who received at least 1 dose of Prolia. Context for the large post-marketing commitment study in the United States (Study 20090522) of similar methodology to the current study.

- **Setting**

The setting includes all medical care delivered by the public health care system in Taiwan. Osteoporosis therapies, including Prolia, are available to both women and men with or without glucocorticoid exposure who have had vertebral or hip fractures related to low BMD through the reimbursement scheme of the Bureau of Health Insurance in Taiwan.

- **Subjects and Study Size, Including Dropouts**

Eligible patients included all men and women 18 years of age or older who had received their first administration of Prolia between 2012 and 2019 and had at least 2 glucocorticoid prescriptions during their first Prolia dose course. Patients were excluded from the study if they had history of malignancy or Paget's disease within 1 year before initial use of Prolia.

For the primary objectives, the dataset for the safety analyses included 27 216 patients and the dataset for the effectiveness analyses included 25 471 patients. For the exploratory objective, the dataset for analysis included 96 patients with an available BMD value at both baseline and during follow-up.

- **Data Source(s) and Methods**

For the primary objectives of safety and effectiveness, the data source was the Health Insurance Research Database (HIRD) of the Taiwan Bureau of Health Insurance. Data

through the year 2020 was included in the study. As the Taiwan Bureau of Health Insurance serves nearly all 23.6 million residents of Taiwan through a single-payer health insurance program, the data source for medical and dental care is population-based (ie, representative of all Taiwan).

For the exploratory objective of change in BMD, the data source was the electronic health records of Chang Gung Research Database (CGRD). Chang Gung is a medical care system providing approximately 10% of all healthcare in Taiwan. This data source provided the clinical information including BMD that was not available in the larger HIRD.

In the evaluation of clinical effectiveness, the incidence rates for the clinical fracture endpoints were calculated as the number of patients with fracture events per 100 person-years of follow-up. Propensity score (PS) matching for known covariates was used to estimate hazard ratios (HRs) and 95% CI for the comparison of fracture incidence rates between the on-treatment and off-treatment cohorts. The analytical strategy to assess the potential of bias due to unmeasured confounding variables included five sensitivity analyses: high dimensional propensity score, rule-out method, E-value, negative control, and ascertainment of unmeasured variables for a subgroup of study population.

In the characterization of safety, the incidence rates for the three safety endpoints were calculated as the number of patients with events meeting the case definition per 10 000 person years of follow-up.

In the exploratory description of changes in BMD, the mean percentage change from baseline in lumbar spine BMD was calculated for the patients with available baseline and follow-up BMD during treatment course with Prolia.

- **Results**

In the evaluation of effectiveness, 559 patients had a hip fracture and the crude incidence rates of hip fracture were 0.94 events and 1.66 events per 100 person-years in the on-treatment and off-treatment cohorts, respectively. With use of PS matching, all baseline clinical characteristics were balanced (standardized mean difference $\geq$ -0.1 to $\leq$ 0.1) between the on-treatment and off-treatment cohorts. In the analysis of the PS matched cohorts, Prolia reduced the risk of hip fracture by 37% (HR = 0.63 [95% CI: 0.52 - 0.77]). The risk reduction was not explained by unmeasured confounding through a series of 5 sensitivity analyses. Risk reductions of similar magnitude were observed for the fracture endpoints of clinical vertebral fracture, and nonvertebral fracture.

In the characterization of safety endpoints, including all patients who received at least 1 dose of Prolia, the observed incidence rates of osteonecrosis of the jaw (ONJ), hypocalcemia, and atypical femur fracture (AFF) were 20.4, 8.1, and 17.9 cases per 10 000 person-years, respectively.

In the exploratory description of Prolia efficacy to increase BMD at the lumbar spine, the mean percent change in BMD was 6.36% (95% CI 3.37 - 9.35) at a mean follow-up of approximately 22 months of therapy.

Discussion

The magnitude of fracture risk reduction observed in this real-world study among more than 20 000 Chinese osteoporosis patients with glucocorticoid exposure and treated with Prolia were consistent with the magnitude of risk reductions demonstrated of Prolia in the international, randomized, placebo-controlled, phase 3 trial among postmenopausal women with osteoporosis (Cummings SR et al, 2009) and consistent with the magnitude of risk reductions observed in the prior real-world studies among Chinese postmenopausal women with osteoporosis (Lai ECC et al, 2022) and among Chinese men with osteoporosis (Study 20210040). Unmeasured confounding, assessed through a series of sensitivity analyses, did not appear to affect interpretation of the current study. The incidence rates of ONJ, AFF, and hypocalcemia in this real-world study among Chinese osteoporosis patients with glucocorticoid exposure and treated with Prolia were consistent with the incidence rates observed in the global post marketing safety study of Prolia that includes osteoporosis patients with glucocorticoid exposure (Study 20090522) and the incidence rates in the prior real-world studies in the prior real-world studies among Chinese postmenopausal women with osteoporosis (Lai ECC et al, 2022) and among Chinese men with osteoporosis (Study 20210040).

In conclusion, based upon these results of this study that provided a direct measure of clinical effectiveness and safety among Chinese osteoporosis patients with glucocorticoid exposure and treated with Prolia, it is expected that the benefit:risk profile of Prolia 60 mg subcutaneously every 6 months in China will be consistent with the global benefit:risk profile.

- **Marketing Authorization Holder(s)**

Amgen Inc.