1. ABSTRACT

- **Title**

Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases

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- **Keywords**

US Medicare, postmenopausal osteoporosis, comparative safety analysis, risk ratio, cumulative risks.

- **Rationale and Background**

As a commitment to the European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) following approval of Prolia® (denosumab) on 26 May 2010 and 01 June 2010, respectively, Amgen developed Study 20090522, "Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in Multiple Observational Databases" as 1 component of the Prolia pharmacovigilance program. This study was conducted each year using large administrative health data systems in the US (US Medicare and Optum Research databases), Denmark, Norway, and Sweden (Aarhus University). The study was designed to accumulate up to 10 years of data after the international birth date of Prolia (26 May 2010) in each data system, dependent on data availability. The study provided descriptive analyses in the real-world postmarketing environment of patient characteristics, utilization patterns, and incidence rates of 9 adverse events of special interests (AESIs) in patients with osteoporosis treated with denosumab. Outcomes included algorithm identified osteonecrosis of the jaw; atypical femoral fracture; fracture healing complications; hypocalcemia leading to hospitalization or emergency room (ER) visit; infections leading to hospitalization or ER visit, dermatologic adverse events leading to hospitalization or ER visit; acute pancreatitis leading to hospitalization; hypersensitivity leading to hospitalization or ER visit; and new primary malignancy (excluding nonmelanoma skin cancer). Osteonecrosis of the jaw and atypical femoral fracture events were confirmed in all denosumab users and in a 1:1 propensity score-matched sample of bisphosphonate (BP) users in select locations.

This is the final study report that primarily focuses on presenting the design, methods, and new results of the comparative safety analyses for study objective 3 as mentioned below. This report also provides an executive summary of the descriptive findings from the amended Year 11 annual report in Section 10.1. The full amended Year 11 annual report is included in Annex 4 of this report. The updated Year 11 report contains the final cumulative descriptive analyses which included the results for 5 of the 6 study objectives listed below (objectives 1, 2, 4, 5, and 6). All previous annual reports have been sent to the EMA and US FDA. The 11th annual report was submitted in December 2022 but at that time, results for confirmed cases of osteonecrosis of the jaw and atypical femoral fracture from Denmark and Sweden were not included due to difficulties in accessing medical records, queues, and prioritization on the Health Department Servers. These results were included in the amended Year 11 report.

Study Objectives

1. Determine incidence rates of AESI in women with PMO exposed to denosumab, women with PMO exposed to BPs, and among all women with PMO.

2. Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to BPs, and all women with PMO.
3. Compare the incidence of the AESIs in women with PMO exposed to denosumab to that in women with PMO exposed to BPs.
4. Describe incidence rates of AESI in postmenopausal women.
5. Describe denosumab utilization patterns in subjects who received denosumab therapy for treatment of PMO.
6. Describe Prolia utilization patterns in subjects who received Prolia therapy for unapproved indications.

The descriptive results from the concluding Year 11 annual report were consistent with the known product safety and benefit-risk profile of Prolia (Annual Report Year 11 amendment, Annex 4).

- **Research Question and Objectives**

The question under investigation was whether the use of denosumab increases the risk of selected AESIs. The complete list of objectives for this study is provided in the above section. For objective 3, the study assessed if the incidence of 7 AESIs (listed below) was comparable among women with PMO initiating denosumab and women with PMO initiating zoledronic acid.

The detailed objectives of the comparative safety analyses are presented below.

Primary Objectives

a) To describe the prevalence of baseline covariates by treatment group
b) To assess comparability of baseline-measured characteristics between treatment groups, after inverse probability of treatment weighting (IPTW) adjustment. Comparability was assessed using standardized mean differences.
c) To evaluate the primary etiologic question of whether denosumab has a biologic effect on the following AESIs, the study assessed the relative risk with 95% CIs among postmenopausal women with osteoporosis who initiated treatment with denosumab and those who initiated treatment with zoledronic acid.

Adverse Events of Special Interest

- Fracture healing complications
- New primary malignancy (excluding nonmelanoma skin cancer)
- Hypocalcemia leading to hospitalization or ER visit
- Infections leading to hospitalization or ER visit, or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization
- Hypersensitivity leading to hospitalization or ER visit.

Secondary Objective

a) To assess the risk difference and 95% CI of the above mentioned AESIs among postmenopausal women with osteoporosis who initiated treatment with denosumab and those who initiated treatment with zoledronic acid if a relative association (95% CI excluded null) exists to better characterize the public health impact of the association.

Oral BP comparator arms using the naïve user design and osteonecrosis of the jaw and atypical femoral fracture AESIs outcomes were also evaluated as exploratory analyses.

The details of these analyses are provided in Section 13.10.5.7.2.6.5 of Protocol Amendment 13 (Annex 2).

- **Study Design**

The comparative safety analysis was conducted within the 20090522 retrospective cohort study using secondary data. A naïve user as-treated design was employed for the primary objective to evaluate if denosumab increases the risk of 7 AESIs compared with the comparator. A naïve user design had the advantage of ensuring the correct temporal assessment between exposure and covariates, capturing early events following initiation, and aligning eligibility, exposure, and start of follow-up.

The active comparator arms were selected based on results from 3 studies that used negative control outcomes to assess the comparability of osteoporosis treatments after adjustment for measured confounders. Zoledronic acid was selected as the comparator of least concerns for confounding in the naïve user design.

- **Setting**

The study population was a sample of the PMO study population included in the Medicare database as part of the postmarketing Study 20090522. Due to power considerations, the comparative analysis was restricted to US Medicare data.

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

  Patients:

Women eligible for inclusion met the criteria for PMO specified in the 20090522 study. For the comparative safety analysis, additional eligibility criteria were required:

- Administration/prescription/dispensing of denosumab or zoledronic acid.
- Cohorts
  - Naïve user (osteoporosis treatment naïve): The treatment initiation index date was the first administration/prescription/dispensing of denosumab or zoledronic acid on or after the Study 20090522 PMO index date and occurring between 30 September 2011 through 31 December 2017. Patients with < 455 days of continuous health plan enrollment preceding the index date were excluded. Zoledronic acid was given yearly; a 455 day (ie, 15 month) minimal look-back period enabled assessment of past use of zoledronic acid and any BP use to determine whether a patient was a naïve user. If more baseline data were available, the look-back period was to be extended further.
  - Patients were excluded for evidence of prior use (previous claim within available historical claims; no maximum time between medications) of any type of osteoporosis drug (eg, BPs, denosumab, teriparatide, or raloxifene).
  - The index date (for description of baseline covariates and start of risk) for the fracture healing complications cohort was the date of the first closed hip fracture that occurred after treatment initiation in the naïve user cohort before 01 January 2018. Restricting the analysis only to patients that experienced a closed hip fracture reduced potential confounding by fracture location and severity. However, if the number of fracture healing complication events was lower than 30 events across both treatment groups, the cohorts were expanded to include fractures occurring at other locations including those near the hip (other femoral fracture closed and closed pelvic fractures) and humerus (Mills 2017; Zura 2017).

Women were excluded from the analysis if they had any of the following conditions or received any of the following treatments on or during the 455 days preceding the naïve

user index date (the baseline period): Paget's disease of bone, cancer (excluding nonmelanoma skin cancer), treatment with chemotherapy, hormonal therapy for cancer, radiation or radiation therapy for cancer, or had prevalent specific AESI during baseline.

Study Size

All available Study 20090522 PMO Medicare data from 26 May 2006 through 31 December 2019, with patients entering the exposure cohort from 30 September 2011 through 31 December 2017 were used in this study. This allowed for a minimum 15-month baseline period and available for up to 24 months of follow-up, although 24 months of follow-up was not required.

- **Data Sources and Statistical Methods**

Medicare data, based on sample size and power, was the most fit-for purpose data set to conduct the 20090522 comparative safety analysis. Medicare data through 31 December 2019 were used in this analysis.

To compare the risk of outcomes between patients who initiated denosumab and patients who initiated zoledronic acid in the primary comparison, and patients who initiated denosumab and patients who initiated oral or any BP in the exploratory comparisons, the baseline characteristics were used to create propensity scores. Sufficient comparability of baseline-measured characteristics based on quantitative assessment of balance in covariates after inverse probability of treatment weights was assessed between the 2 exposure groups. Adjusted cumulative risks were calculated by each treatment group using inverse probability of treatment and censoring weight estimation functions. Adjusted cumulative risk by treatment (with 95% CIs) were plotted and adjusted 1-year risk ratios (RRs) (and corresponding 95% CIs) were tabulated for each AESI for the primary objective. Adjusted risk differences (and corresponding 95% CIs) were tabulated for the secondary objective if relative associations (95% CI excludes null) were observed. Programmers and analysts were separated from investigators who were blinded from the study exposures and the decision made at each step of analytical process was documented by the external investigators.

- **Results**

Comparative Safety Analyses

Primary Comparison (Denosumab vs Zoledronic Acid)

- At 1 year, no increased risk (RR < 1 or 95% CIs included null value of 1) was observed in the primary comparison of denosumab vs zoledronic acid users for the following AESIs: acute pancreatitis leading to hospitalization, dermatologic adverse events leading to hospitalization or ER visit, hypersensitivity leading to hospitalization or ER visit, infections leading to hospitalization or ER visit or administration of parenteral anti-infective medication, hypocalcemia leading to hospitalization or ER visit, new primary malignancy (excluding nonmelanoma skin cancer), fracture healing complications), and exploratory outcome of atypical femoral fracture.
- There was some indication of higher risk of hypocalcemia in denosumab vs zoledronic acid users; however, the 95% CI included the null value (RR 1.89; 95% CI 0.79, 3.00).
- At 1 year, no increased risk was observed in the primary comparison of denosumab vs zoledronic acid users for osteonecrosis of the jaw (RR 1.08 95% CI 0.54, 1.63).
- The number of events of atypical femoral fracture were small (< 11), providing imprecise estimates with wide confidence intervals that include the null value and with the lower bound including zero (RR 2.82, 95% CI 0.00, 8.81), making the results difficult to interpret.

Exploratory Comparisons (Denosumab vs Oral BP; Denosumab vs Any BP)

- At 1 year, no increased risk (RR < 1 or 95% CIs included null value of 1) was observed in the exploratory comparisons of denosumab vs oral or any BP users for the following AESIs: new primary malignancy (excluding nonmelanoma skin cancer), infections leading to hospitalization or ER visit or administration of parenteral anti-infective medication, dermatologic adverse events leading to hospitalization or ER visit, acute pancreatitis leading to hospitalization, hypersensitivity leading to hospitalization or ER visit, fracture healing complications, and exploratory outcome of atypical femoral fracture.
- At 1 year, a higher risk of hypocalcemia was observed in the denosumab users in both the oral BP (RR 6.96; 95% CI 3.57, 10.35) and any BP (RR 5.84; 95% CI 3.42, 8.27) comparisons.
- At 1 year, a higher risk of osteonecrosis of the jaw was observed in the denosumab users in both the oral BP (RR 1.45; 95% CI 0.99, 1.92) and any BP (RR 1.48; 95% CI 1.02, 1.93) comparisons.
- A small number of events (< 30 across exposure cohorts) were observed for atypical femoral fracture. While the low number of events overall is reassuring, it resulted in imprecise estimates. However, there was no evidence of an increased risk in the denosumab users (denosumab vs oral BP comparison RR 0.79, 95% CI 0.08, 1.51 and denosumab vs any BP comparison RR 0.88, 95% CI 0.09, 1.67) at 1 year.

- **Conclusion**

The results of the comparative safety analyses provide information on the safety profile of denosumab relative to BP therapies. Overall, the results of this study were consistent with the known safety profile of denosumab.

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