1. ABSTRACT

- **Title**

A Non-interventional Pharmacovigilance Study of Osteonecrosis of the Jaw and Infection Leading to Hospitalization Among Patients With Cancer Treated With XGEVA® or Zoledronic Acid in Sweden, Denmark, and Norway (Study 20101363). 7 January 2020. [redacted], Denmark

- **Keywords**

Antiresorptive treatment, postauthorization safety study; epidemiology; osteonecrosis of the jaw.

- **Rationale and Background**

XGEVA® (denosumab 120 mg subcutaneously every 4 weeks [Q4W]) is currently approved for the prevention of skeletal-related events in adults with advanced malignancies involving bone. Osteonecrosis of the jaw (ONJ) is an important adverse event of antiresorptive treatment. Serious infection is an important concern in patients with advanced cancer. The study was designed to estimate the incidence proportions of medically confirmed ONJ and infection leading to hospitalization. This study is a postauthorization commitment to the European Medicines Agency (ClinicalTrials.gov registration number NCT01967160).

- **Research Question and Objectives**

The primary objectives were:

- To estimate, by treatment cohort, the 1-, 2-, 3-, 4-, and 5-year incidence proportions and 95% confidence intervals (CIs) of medically confirmed ONJ among patients with cancer whose initial antiresorptive treatment was XGEVA® or IV zoledronic acid (Zometa® or generic zoledronic acid in cancer doses; hereafter, the XGEVA and zoledronic acid inception cohorts);
- To estimate, by treatment cohort, the 1-, 2-, and 3-year incidence proportions and 95% CIs of infection leading to hospitalization in the XGEVA and zoledronic acid inception cohorts.

The secondary objectives were:

- To estimate the 1-, 2-, 3-, 4-, and 5-year incidence proportions and 95% CIs of medically confirmed ONJ in cancer patients who started cancer-related antiresorptive treatment with any oral or IV bisphosphonate at the doses indicated to prevent skeletal-related events (SREs) and switched to XGEVA® (hereafter, the XGEVA-switch cohort);
- To estimate the 1-, 2-, 3-, 4-, and 5-year incidence proportions and 95% CIs of medically confirmed ONJ for the XGEVA-switch cohort stratified by the number of prior cancer-related bisphosphonate treatments at the doses indicated to prevent SREs;
- To characterize the XGEVA inception, zoledronic acid inception, and XGEVA-switch cohorts with respect to patient characteristics, cancer site, medical history, and number of bisphosphonate or XGEVA® treatments at the doses indicated to prevent SREs;
- To summarize the oral risk factor information for medically confirmed ONJ cases;

- To summarize the information on ONJ stage, treatment, clinical course, and resolution, for medically confirmed ONJ cases.

- **Study Design**

This was a non-interventional cohort study.

- **Setting**

This study was conducted in Sweden, Norway, and Denmark, all of which are welfare states with universal access to health care.

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

The XGEVA inception cohort was initially estimated to include approximately 900 patients, the XGEVA-switch cohort 150 patients, and the zoledronic acid inception cohort approximately 1,050 patients.

- **Variables and Data Sources**

Potentially eligible patients with a diagnosis of cancer and subsequent initiation of XGEVA® or zoledronic acid were identified using routinely collected data in the relevant, linked population-based registries in Sweden, Denmark, and Norway. Treatment information was ascertained through medical chart review. ONJ was independently ascertained in treating clinics and recorded in the Scandinavian ONJ Cohort. All cases were medically confirmed by an ONJ adjudication committee according to uniform criteria. Data on infections and patient demographic and clinical characteristics originated from each country's national patient registry, national prescription registry, and national cancer registry.

- **Results**

After applying the eligibility criteria, 2,877 patients were included in the analysis: 1,340 in the XGEVA inception cohort, 1,352 in the zoledronic acid inception cohort, and 408 in the XGEVA-switch cohort. Men accounted for 72.6% of the XGEVA inception cohort; 53.8% of the zoledronic acid inception cohort, and 48.3% of the XGEVA-switch cohort. The respective median age in the three cohorts was 70.4, 68.9, and 70.2 years. The 5-year incidence proportions (95% CI) of medically confirmed ONJ were 5.7% (4.4, 7.3) in the XGEVA inception cohort; 1.4% (0.8, 2.3) in the zoledronic acid inception cohort, and 6.6% (4.2, 10.0) in the XGEVA-switch cohort. Among the medically confirmed ONJ cases, 58.3% of the patients had a history of oral trauma, including 54.2% with a history of extraction or oral surgery. ONJ had resolved at the time of the latest examination in 34.2% of the cases. The 3-year incidence proportions (95% CI) of infection leading to hospitalization were 28.9% (26.5, 31.4) in the XGEVA inception cohort, 22.5% (20.3, 24.8) in the zoledronic acid inception cohort, and 22.8% (18.8, 27.2) in the XGEVA-switch cohort.

- **Discussion**

In Sweden, Denmark, and Norway, the 5-year incidence proportions of medically confirmed ONJ among cancer patients with bone metastases treated for prevention of SREs in routine clinical practice were higher in patients initiating XGEVA® (5.7%, 95% CI: 4.4, 7.3) than in patients initiating zoledronic acid (1.4%, 95% CI: 0.8, 2.3). The 5-year incidence proportion of ONJ in patients switching from XGEVA® to zoledronic acid was 6.6% (95% CI: 4.2, 10.0). The corresponding 3-year incidence proportions of serious infection were 28.9% (95% CI: 26.5, 31.4), 22.5% (95% CI 20.3, 24.8) and 22.8% (95% CI: 18.8, 27.2).

The main limitation of this study an inherent absence of comparability between patients in the treatment cohorts, which is typical of newly marketed medications and precludes meaningful comparative analysis (Schneeweiss et al. 2011) . Also the criteria for clinical diagnosis of ONJ have changed over time and the incidence proportions of ONJ and infection are biased downwards in the presence of censoring. Finally, completeness of ascertainment of ONJ varied by country, with some evidence of greater completeness in Denmark thanks to centralized nature of ONJ treatment.

These findings are consistent with other evidence.

- **Marketing Authorization Holder(s)**

Amgen Inc

- **Names and Affiliations of Principal Investigators**
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