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LETTER TO THE EDITOR

Response to letter to the Editors—Safety of long-term denosumab therapy

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Dear Editors,

We would like to thank Drs. Fusco, Bedogni, Addeo, and Campisi [1] and Drs. Boissieu and Trenque [2] for their interest and review of our study report [3].

Our long-term safety study [3] was based on denosumab exposure (Q4W, 120 mg SC dosing) and focused on the identification of any new safety signals as well as known adverse events such as osteonecrosis of the jaw (ONJ) in patients with either advanced breast or prostate cancer. The data were taken from the primary skeletal-related events (SRE) trials [4, 5] and their respective open-label extension (OLE) phases (up to 2 additional years). Adverse events were monitored and potential ONJ events were adjudicated by an independent committee of oral surgeons and dentists [4, 5]. Patient-year adjusted event rates of adjudicated positive ONJ were summarized.

In the first Letter To The Editor by Fusco et al., the authors comments are as follows:

1) *Provide clarity of median denosumab exposure.*

As originally described in Stopeck et al. [3], the median denosumab exposure (range) for the primary and the OLE phases combined was 19.1 months (0.1–59.8 months) for the breast cancer population (n = 1019) and 12.0 (0.1–67.2 months) for the prostate cancer population (n = 942). There was some confusion by Fusco et al. on the length of time for the median denosumab exposure of the OLE phase only, which we originally reported in Stopeck et al. [3] as 17.6 months (0–23.7 months) for the breast cancer population (n = 318) and 12.0 months (0.1–23.3 months) for the prostate cancer population (n = 147).

2) *Clarify why the ONJ rates reported in the OLE safety manuscript are higher than what was originally reported for the primary analyses of the primary SRE studies.*

The higher reported ONJ rates in the OLE safety manuscript [3] are due to the higher cumulative exposure of the respective antiresorptive treatment. For example, the denosumab/denosumab patient group (n = 318 for breast and n = 147 for prostate cancer) in the OLE analysis was exposed to denosumab during the blinded treatment phase until the completion of the blinded treatment phase, with additional denosumab exposure in the OLE phase for up to 2 years. Therefore, the median cumulative denosumab exposure was 43.0 months for breast cancer (n = 318) and 36.9 months for prostate cancer (n = 147) groups. The resulting ONJ rates are higher for these denosumab/denosumab patients in the OLE phase of these two studies, which are expected and consistent with the observation that ONJ risk increases with longer exposure of denosumab as documented in the XGEVA® prescribing information [6]. The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of denosumab treatment, 3.7% in the second year, and 4.6% per year thereafter. The ONJ rates reported in Table 3 of the OLE safety manuscript are the rates for the OLE phase only. For both primary SRE studies, patients who had positively adjudicated ONJ during the blinded treatment phase were not enrolled in the OLE phase.

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3) *What were the guidelines used for determining positively adjudicated ONJ at the time of analysis*?

The methodology used to determine which cases of ONJ were sent for adjudication was based on a search using clinical terms from the MEDRA guidelines at the time of the study. In our study, the breast cancer patients/denosumab arm had 119 patients with potential ONJ and 48 patients that were positively adjudicated. For the zoledronic acid arm, 93 patients were identified with potential ONJ and 35 patients were positively adjudicated. For the prostate cancer patients/denosumab arm, 75 patients were identified with potential ONJ and 36 patients were positively adjudicated. For the zoledronic arm, 54 patients were identified with potential ONJ and 21 were positively adjudicated. However, as mentioned by Fusco et al., AAOMs [7] updated and broadened the definition of ONJ in 2014, which was *after* the collection of ONJ data from our primary and OLE phases of the study.

4) *Suggestion for an analysis of the OLE subset only* (*Fusco et al.*) *as compared to the analysis of the combined primary and OLE subsets as presented in Stopeck et al.* [3].

The primary goal of the Stopeck et al. manuscript [3] was to provide a comprehensive safety summary for both the breast and prostate cancer patient populations based on the primary SRE studies and OLE data. The specific analysis suggested by Fusco et al. would look at a narrow subset of OLE patients who have not experienced ONJ over a certain period of exposure and their risk in further exposure to denosumab. Although interesting, this was not the aim of the manuscript and has inherent limitations which could obscure and possible mislead clinical interpretation.

In the second Letter To The Editor by Boissieu et al., the authors comments are as follows:

1) *In regards to the reported number of positively adjudicated ONJ patients*, *clarify the differences between what was reported in the primary SRE trials for breast* [4] *and prostate* [5] *cancer patients and what was reported in the current*, *Stopeck et al. safety manuscript* [3].

In both the primary SRE trial manuscripts [4, 5], the number of positively adjudicated ONJ cases was reported up to the primary analysis (PA) cutoff date of 06-Mar-2009 for the breast cancer and 30-Oct-2009 for the prostate cancer trials. For the Stopeck et al. safety manuscript [3], the total number of positively adjudicated ONJ cases (breast and prostate cancer patients) during the blinded treatment phase refers to the data up to the end-of-blinded treatment phase (DBE) cutoff date (20-Jul-2009 for the breast and 26-Feb-10 for the prostate cancer trial), which occurred approximately 4 months after the PA cutoff date. The DBE time period is where the additional, positively adjudicated ONJ cases were accrued for both the denosumab and zoledronic arms when compared to the primary SRE trials. In the breast cancer trial, the numbers of positively adjudicated ONJ cases in denosumab arm vs zoledronic acid arm were 20 (2.0%) vs 14 (1.4%) by PA cutoff and increased to 26 (2.5%) vs 18 (1.8%) by DBE cutoff. In the prostate cancer trial, the numbers were 22 (2.3%) and 12 (1.3%) by PA cutoff and increase to 23 (2.4%) and 13 (1.4%) by DBE cutoff. In both trials, ONJ rates were not statistically higher for denosumab compared with zoledronic acid based on the data up to DBE. This conclusion is consistent with results based on PA data as reported in the original PA for the breast and prostate cancer populations [4, 5].

We agree that patients on antiresorptive therapies should be diligently monitored for oral complication, encouraged to practice good oral hygiene, and referred to a trained dental health professional for dental symptoms.

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Compliance with ethical standards

Conflict of interest Alison Stopeck (MD) served as a consultant for Amgen Inc., Pfizer, Bayer, Genentech, and Clovis Pharmaceuticals. She received research funding from Amgen Inc., Novartis, Peregrine, Puma, and Bayer. Douglas Warner (MD) is an Amgen Inc. employee and has received Amgen Inc. stocks.

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