1. ABSTRACT

- **Title**

  Effectiveness, efficacy, and safety of XGEVA®/ANJIAWEI® (denosumab) in Chinese patients with Giant Cell Tumor of Bone (GCTB): a systematic literature review

- **Keywords**

  XGEVA®/ANJIAWEI®, Giant Cell tumor of bone, GCTB, systematic review, China

- **Rationale and Background**

  Globally, clinical and real-world evidence suggests that XGEVA®/ANJIAWEI® is both safe, efficacious, and effective for the treatment of adults and skeletally mature (defined as at least 1 mature long bone and body weight ≥ 45 kg) adolescents with giant cell tumor of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity. However, because of the limited generalizability of Clinical Trial evidence specifically for the Chinese GCTB patient population, Amgen sought a current review of published evidence among Chinese GCTB patients to better understand the benefit-risk of XGEVA®/ANJIAWEI®. This assessment will be informed by clinical and real-world evidence (RWE) from publicly available literature, relevant to establishing an understanding of the safety and effectiveness of XGEVA®/ANJIAWEI® in Chinese patients with GCTB.

- **Research Question and Objectives**

  The aim of this systematic review was to evaluate published evidence on the safety and clinical effectiveness of XGEVA®/ANJIAWEI® among mainland Chinese and Chinese patients in Taiwan, Hong Kong, and Macau with GCTB, and to characterize the benefit-risk profile associated with use of this drug in Chinese GCTB patients, in the context of the global body of evidence derived from XGEVA®/ANJIAWEI® treated GCTB patients.

- **Study Design**

  A systematic literature review (SLR) was conducted to identify conference abstracts, and peer reviewed case series, reports, and publications of randomized and observational studies, as well as dissertations and master theses, that reported on disease progression, recurrence, response rate, surgical downgrading, limb, or joint complications requiring surgery, and any safety endpoints, in individuals diagnosed with Giant Cell Tumor of Bone (GCTB). Publications were identified up through October 2022.

- **Setting**

  This SLR was conducted to identify published studies of XGEVA®/ANJIAWEI® for treatment of GCTB among skeletally mature Chinese adolescents (ages ≥ 12 years) and adults in China, including mainland China, Taiwan, Hong Kong, and Macau. No restrictions were placed on study design (randomized, observational), and studies with or without non-denosumab comparison groups were eligible for inclusion.

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

  A literature search was conducted from 12 September 2022 to 16 September 2022 in Simplified Chinese, Traditional Chinese, and English, using the corresponding language terms for GCTB and XGEVA®/ANJIAWEI® (denosumab) mapped to subject headings, in CNKI, 万方 (Wanfang Med), and 维普(cqvip), NCL Taiwan Periodical Literature, Airiti Library, Pubmed/MEDLINE, Epub Ahead of Print and In-

Process & Other Non-Indexed Citations, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Web of Science BIOSIS Preview, TRIP, and Google Scholar.

A total of six reviewers, in pairs of two, independently reviewed and screened titles and abstracts, and selected the identified records for full-text review: two reviewers for publications in Simplified Chinese, two reviewers for publications in Traditional Chinese, and two reviewers for publications in English. The articles that were identified via the title/abstract screening process were retrieved, translated into English as needed, and reviewed by the team of English-Language reviewers for study eligibility and inclusion according to PICOS criteria. Disagreements between reviewers during title/abstract screening were resolved after full-text review by consensus discussion and consultation with an independent seventh reviewer with clinical expertise in GCTB, who made the final decision. The Downs and Black checklist for assessment of methodological quality of randomized and non-randomized studies was used to assess bias. The 27-item checklist, which is based upon quality of reporting, external validity, internal validity (bias and confounding) and statistical power, was imported into the Data Extraction and Quality Assessment Form for ease of use with the included studies during the review process.

- **Results**

  Thirty-Nine studies (1 randomize clinical trial (RCT), 1 prospective cohort study, 18 retrospective cohort studies, and 19 case series/reports) were included in this SLR, of which twelve (30.7%) were published in Simplified Chinese, twenty-five (64.1%) in English, and two in Simplified Chinese and English. Of the thirty-nine studies, thirty-six (92.3%) were conducted in mainland China. Respectively, 89.7% studies reported on the use of neoadjuvant denosumab, while 41% reported on adjuvant use of denosumab.

  Denosumab therapy was administered in accordance with the recommended dosing schedule of 120 mg every 4 weeks with loading doses on days 1, 8 and 15. Although there were no observed deviations in the dosing (mg) of denosumab, there were observed variations in the number of doses administered in the neoadjuvant setting and adjuvant setting. The mean number of neoadjuvant administrations was 3 to 6 among studies that reported doses, and mean length of treatment was 1 to 5 months before surgical procedures. Adjuvant denosumab ranged from 7 to 14 doses for durations up to 2 years post-operatively.

  Twenty-two studies reported recurrence or recurrence free-survival rates (percentages) in relation to neoadjuvant (N=21) or adjuvant-only denosumab (N=5). Most (N=20) were retrospective cohorts, but the neoadjuvant studies included one prospective cohort and one RCT. Among studies with $>$ 10 patients who received neoadjuvant XGEVA®/ANJIAWEI® (N=15), recurrence rates were between 4.8% and 27.4%. Four of six studies with $\leq$ 10 neoadjuvant denosumab patients observed zero cases of recurrence over $\geq$ 12 months of follow-up. Eight studies compared neoadjuvant denosumab treatment to a non-denosumab referent or control group. Of these, six found lower recurrence in the denosumab-treated compared to the control group. Recurrence rates among adjuvant-only exposed denosumab patients ranged between 0% to 22.2%, with time to recurrence between 18.3 to 95 months.

Objective response rate (ORR) was reported in seven studies and ranged between 43.8% to 100% among patients who received neoadjuvant denosumab. One study reported ORR of 42.9% among patients with pulmonary metastasis who were treated post-operatively, and another study observed ORR of 56% among patients with unresectable disease. Strong radiologic response and/or histologic decrease or clearance of GCTB were widely reported in relation to denosumab treatment.

Clinical response with improvement in pain and functioning was frequently observed. Four studies reported a statistically significant change in the improvement of mean visual analogue scale (VAS) score before and after denosumab of between -3.3 and -4.6, respectively.

No new safety concern was reported in any study with denosumab administration. Eleven studies specifically reported on the development of ONJ. Of these 11 studies, 10 studies observed no cases of ONJ. Three of seven studies reported no observed hypocalcemia, and two of three studies reported no atypical femoral fracture (AFF). Five studies that did not report specifically on ONJ, hypocalcemia, or AFF, reported no observed serious adverse events.

- **Discussion**

  The available clinical and epidemiologic evidence on the safety and effectiveness of denosumab for treatment of GCTB among patients in mainland China and Chinese population appears consistent with the global body of evidence for the known safety and efficacy profile of denosumab in this indication. This systematic review of the literature synthesizing the results of GCTB retrospective studies, case series, case reports, and a large multi-center randomized controlled trial, from hospitals across mainland China, Taiwan, and Hong Kong, consistently demonstrates effective disease control, clinical benefit, and acceptable tolerability in the Chinese GCTB patient population. This benefit-risk profile supports the continued use of XGEVA®/ANJIAWEI® for the treatment of Chinese GCTB patients in the neoadjuvant and adjuvant setting in mainland China.

- **Marketing Authorization Holder(s)**

  Amgen, Inc

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