



## Amgen Presents New Data From Phase 3 XGEVA® (denosumab) Study In Multiple Myeloma Patients At The 16th International Myeloma Workshop

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### Results to be Presented as Late-Breaking Oral Presentation Largest International Trial Conducted in Multiple Myeloma Study Met Primary Endpoint of Non-Inferiority Versus Zoledronic Acid in Delaying Bone Complications Known as Skeletal-Related Events

THOUSAND OAKS, Calif., March 3, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced positive data from the Phase 3 '482 study, the largest international multiple myeloma trial ever conducted. In this study, XGEVA® (denosumab) met the primary endpoint, demonstrating non-inferiority to zoledronic acid in delaying the time to first on-study skeletal-related event (SRE) in patients with multiple myeloma (HR=0.98, 95 percent CI: 0.85, 1.14;  $p=0.01$ ). The median time to first on-study SRE was similar between XGEVA (22.83 months) and zoledronic acid (23.98 months). These data will be presented today during the late-breaking abstract session at the 16<sup>th</sup> International Myeloma Workshop (IMW) in New Delhi.

"Bone complications are devastating for patients with multiple myeloma. Renal function is a constant consideration in the treatment of multiple myeloma patients, often preventing the use of bisphosphonates, the only approved class of agents for prevention of bone complications, underscoring the need for new treatment options," said Noopur Rajee, M.D., director, Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston. "The results of this study showed that denosumab may be an effective novel option that is not cleared through the kidneys that may help prevent bone complications in patients with multiple myeloma."

The secondary endpoints of superiority in delaying time to first SRE and delaying time to first-and-subsequent SRE were not met in this study. There was a suggested trend in overall survival (OS) in favor of XGEVA over zoledronic acid (HR=0.90, 95 percent CI: 0.70, 1.16;  $p=0.41$ ); however, it was not statistically significant. The hazard ratio of XGEVA versus zoledronic acid for progression-free survival (PFS) was 0.82 (95 percent CI: 0.68, 0.99; descriptive  $p=0.036$ ). The median PFS difference between arms was 10.7 months in favor of XGEVA.

"XGEVA is currently approved for the prevention of bone complications in patients with solid tumors based on superior clinical benefits over zoledronic acid in this setting," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "The results being presented today reinforce that XGEVA's unique mechanism of action and subcutaneous administration may also offer patients with multiple myeloma a valuable alternative to the current standard of care. Amgen plans to submit these results to regulatory agencies worldwide to support a potential update to the XGEVA label."

Adverse events observed in patients treated with XGEVA were consistent with the known safety profile of XGEVA. The most common adverse events (greater than 25 percent) were diarrhea (33.5 percent XGEVA and 32.4 percent zoledronic acid) and nausea (31.5 percent XGEVA and 30.4 percent zoledronic acid).

Multiple myeloma is the second most common hematologic cancer, and it develops in plasma cells located in the bone marrow microenvironment.<sup>1,2</sup> Bone lesions appear in the vast majority of patients with multiple myeloma and weaken the bone.<sup>3</sup> Myeloma cells induce RANK ligand (RANKL) expression, a protein essential for the formation, function and survival of osteoclasts, which break down bone. In addition, direct RANKL expression by myeloma cells may enhance osteoclast activity in the bone microenvironment.<sup>4</sup> Excessive RANKL can increase the risk of bone complications, including pathologic fractures, radiation therapy or surgery to the bone, and spinal cord compression.<sup>5,6</sup>

#### About '482 Study (NCT01345019)

The '482 study was an international, Phase 3, randomized, double-blind, multicenter trial of XGEVA compared with zoledronic acid in the prevention of bone complications in patients with newly diagnosed multiple myeloma. In the study, a total of 1,718 patients (859 on each arm) were randomized to receive either subcutaneous XGEVA 120 mg and intravenous placebo every four weeks, or intravenous zoledronic acid 4 mg (adjusted for renal function) and subcutaneous placebo every four weeks. The primary endpoint of the study was non-inferiority of XGEVA versus zoledronic acid with respect to time to first on-study SRE (fracture, radiation to bone, surgery to bone or spinal cord compression). Secondary endpoints included superiority of XGEVA versus zoledronic acid with respect to time to first on-study SRE and first-and-subsequent on-study SRE and OS. PFS was an exploratory endpoint. The safety and tolerability of XGEVA were also compared with zoledronic acid.

#### About Multiple Myeloma and Bone Complications

Multiple myeloma is the second most common hematologic cancer, and it develops in plasma cells located in the bone marrow microenvironment.<sup>1,2</sup> It is characterized by a recurring pattern of remission and relapse, with patients eventually becoming refractory to treatment.<sup>7</sup> Each year an estimated 114,000 new cases of multiple myeloma are diagnosed worldwide, resulting in more than 80,000 deaths per year.<sup>1</sup>

Bone lesions are a hallmark of multiple myeloma and often result in bone complications.<sup>3,6</sup> Additionally, renal impairment is a common complication of multiple myeloma.<sup>8</sup> Approximately 60 percent of all multiple myeloma patients have or will have renal impairment over the course of the disease.<sup>8</sup> Current treatment options including zoledronic acid are cleared by the kidneys and associated with renal toxicity.<sup>6</sup> Preventing bone complications is a critical aspect of caring for patients with multiple myeloma, because these events can cause significant morbidity.<sup>9</sup>

#### About XGEVA® (denosumab)

XGEVA targets the RANKL pathway to prevent the formation, function and survival of osteoclasts, which break down bone. XGEVA is indicated for the prevention of SREs in patients with bone metastases from solid tumors and for treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. XGEVA is also indicated in the United States (U.S.)

for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. XGEVA is not indicated for the prevention of SREs in patients with multiple myeloma.

## **U.S. Important Safety Information**

### **Hypocalcemia**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA. XGEVA can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when XGEVA is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.

An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

### **Hypersensitivity**

XGEVA is contraindicated in patients with known clinically significant hypersensitivity to XGEVA, including anaphylaxis that has been reported with use of XGEVA. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA therapy permanently.

### **Drug Products with Same Active Ingredient**

Patients receiving XGEVA should not take Prolia<sup>®</sup> (denosumab).

### **Osteonecrosis of the Jaw**

Osteonecrosis of the jaw (ONJ) has occurred in patients receiving XGEVA, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with osseous metastasis, the incidence of ONJ was higher with longer duration of exposure.

Patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance are at a greater risk to develop ONJ. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroid, diabetes, and gingival infections.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA and periodically during XGEVA therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA. Consider temporarily interrupting XGEVA therapy if an invasive dental procedure must be performed.

Patients who are suspected of having or who develop ONJ while on XGEVA should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

### **Atypical Subtrochanteric and Diaphyseal Femoral Fracture**

Atypical femoral fracture has been reported with XGEVA. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA therapy should be considered, pending a risk/benefit assessment, on an individual basis.

### **Embryo-Fetal Toxicity**

XGEVA can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA is expected to result in adverse reproductive effects. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least five months after the last dose of XGEVA. Apprise the patient of the potential hazard to a fetus if XGEVA is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA.

### **Adverse Reactions**

The most common adverse reactions in patients receiving XGEVA with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea.

The most common adverse reactions in patients receiving XGEVA for giant cell tumor of bone were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis. The most common adverse reactions resulting in discontinuation of XGEVA were osteonecrosis of the jaw and tooth abscess or tooth infection.

The most common adverse reactions in patients receiving XGEVA for hypercalcemia of malignancy were nausea, dyspnea, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea.

Denosumab is also marketed as Prolia<sup>®</sup> in other indications.

Please visit [www.amgen.com](http://www.amgen.com) or [www.xgeva.com](http://www.xgeva.com) for Full U.S. Prescribing Information.

### **About Amgen's Commitment to Oncology**

Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of

innovative and biosimilar oncology medicines.

## About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit [www.amgen.com](http://www.amgen.com) and follow us on [www.twitter.com/amgen](http://www.twitter.com/amgen).

## Forward-Looking Statements

This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. We or others could identify safety, side effects or manufacturing problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock.

The scientific information discussed in this news release relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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