



## **Integrated Analysis Demonstrates That Denosumab Delays the Onset of Bone Complications Compared to Zometa(R)**

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**Additional Analyses Highlight the Significant Impact of Bone Complications on Pain and Consumption of Health Resources**

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Amgen (Nasdaq:AMGN) today announced results from two integrated analyses of head-to-head pivotal Phase 3 trials comparing denosumab to Zometa(R) (zoledronic acid), the current standard of care in the prevention of skeletal related events (SREs) in patients with advanced malignancies involving bone. In these separate analyses, denosumab demonstrated a clinically meaningful, consistent and robust treatment effect across tumor types in the reduction of SREs, and also prevented clinically relevant increases in pain, compared with Zometa. A separate presentation highlighted the meaningful burden that SREs pose to the healthcare system. These analyses were presented at the 35th European Society for Medical Oncology (ESMO) Congress being held in Milan, Italy.

"Bone metastases and their subsequent complications, such as a fracture, are devastating events for advanced cancer patients and costly to the healthcare system," said Allan Lipton, M.D., professor of Medicine & Oncology, M.S. Hershey Medical Center of the Pennsylvania State University. "This analysis of the largest registration program ever undertaken in bone metastases demonstrates that denosumab can offer a clinical advance over Zometa in delaying or preventing these bony complications, as well as the pain that frequently results from them. These efficacy gains coupled with the convenience of a subcutaneous injection and no need for renal monitoring make denosumab an attractive option for these patients."

### **Integrated Analysis Reveals Denosumab Superior to Zometa In Delaying or Preventing Time to First-and-Subsequent Skeletal Related Event Across a Broad Cancer Population with Bone Metastases**

The effect of denosumab versus Zometa was evaluated in three large, identically designed Phase 3 trials that enrolled patients with bone metastases and breast cancer, prostate cancer or other solid tumors and multiple myeloma. The integrated analysis of these trials, which together enrolled more than 5,700 patients, provided a clear view of the efficacy and safety profile of denosumab in a large and diverse group of people living with cancer and bone metastases.

The analysis showed that denosumab was superior to Zometa in delaying time to first on-study SRE by 17 percent (median time to first skeletal related event of 27.7 months for denosumab and 19.5 months for Zometa,  $p < 0.0001$ ). Denosumab was also superior to Zometa in delaying time to first-and-subsequent on-study SRE by 18 percent ( $p < 0.0001$ ). Overall disease progression and survival were similar for both groups.

Overall, the occurrence of adverse events (96.2 percent denosumab, 96.8 percent Zometa) and serious adverse events (56.3 percent denosumab, 57.1 percent Zometa) were balanced in both groups and consistent with what has previously been reported for these two agents.

Osteonecrosis of the jaw (ONJ) occurred infrequently, 1.8 percent of denosumab patients and 1.3 percent of Zometa patients ( $p=0.13$ ) experienced this adverse effect. In addition, Zometa-treated patients had increased rates of adverse events potentially associated with renal toxicity (2.6 percent higher) and increased rates of acute phase reactions (8.7 percent denosumab, 20.2 percent Zometa). As with previous studies in advanced cancer patients, hypocalcemia was more frequent in the denosumab arm (9.6 percent denosumab, 5.0 percent Zometa).

Patients received either 120 mg of denosumab subcutaneously every four weeks or Zometa administered intravenously as at least a 15 minute infusion at a dose of 4 mg every four weeks, per the labeled instructions.

### **Integrated Pain Analysis Shows Denosumab Superior to Zometa**

A separate integrated analysis of the three Phase 3 trials found that denosumab was superior to Zometa in preventing clinically relevant increases in pain, as reported by trial participants. Bone pain is one of the first signs that metastatic disease has spread to the skeleton, and affects approximately 70 percent of patients with metastatic disease. (i) Patients enrolled in the three studies completed the Brief Pain Inventory (range 0-10) to assess pain severity at baseline (BL), day 8, and monthly through the end of the studies (week 41).

Time to worsening of clinically significant pain was significantly delayed with denosumab compared to Zometa (median of 181 days for denosumab, median of 169 days for Zometa) (hazard ratio 0.92, 95 percent CI 0.86-0.99,  $p=0.026$ ). In patients with no or mild pain at BL, denosumab prolonged the median time until moderate or severe pain by 55 days compared to Zometa (198 days denosumab, 143 days Zometa) (hazard ratio 0.83, 95 percent CI 0.76-0.92,  $P=0.0002$ ). The time to pain improvement was similar in both treatment groups (86 days for denosumab, 85 days for Zometa) (hazard ratio 0.99; 95 percent CI 0.92-1.07;  $p=0.844$ ).

### **Multinational Study Illustrates Resource Utilization Varies by Skeletal Related Event**

SREs have an adverse financial impact on healthcare systems, consuming significant resources. Results from the first interim analysis of a multinational observational study assessing the utilization of health resources by type of SRE showed that pathologic fractures resulted in the longest hospital stay (16.3 days), with both spinal cord compression and radiation to bone resulting in the next longest hospital stay (9.3 days). Meanwhile, radiation to bone resulted in the highest number of outpatient visits (10.0) and overall procedures (e.g., imaging) (13.5).

The ongoing observational, multinational study assessed SRE-related utilization of health resources by SRE type (surgery or radiation to bone, pathologic fracture, or spinal cord compression) in prostate, breast or lung patients with bone metastases, or in patients with multiple myeloma. Data was collected on inpatient hospitalizations, length of stay, outpatient visits, emergency room (ER) visits, nursing home/long-term care facility stays, home health visits, procedures, and medications. This interim analysis included 206 eligible patients with 387 discrete SREs.

## **Bone Metastases and Skeletal Related Events (SREs): Prevalence and Impact**

Bone metastases occur in more than 1.5 million patients with cancer worldwide and are most commonly associated with cancers of the prostate, lung, and breast, with incidence rates as high as 75 percent of patients with metastatic disease.(ii)

Approximately 50-70 percent of cancer patients with bone metastases will experience debilitating SREs.(iii)(iv)(v) Events considered to be SREs include fractures, spinal cord compression, and severe bone pain that may require surgery or radiation(vi). Such events can profoundly disrupt a patient's life and can cause disability, pain or even death. (vii)(viii)(ix)

Patients who experience an SRE as a result of bone metastases incur significantly higher medical costs compared with those who do not experience such events.(x)(xi)(xii) Studies have shown that the costs of treating a SRE are significant.(x)(xiii) In fact, the total economic burden of patients with bone metastases in the U.S. alone is estimated to be \$12.6 billion annually.(xiv)

## **About Denosumab and Amgen's Research in Bone Biology**

Denosumab is the first fully human monoclonal antibody in late stage clinical development that specifically targets RANK Ligand, the essential regulator of osteoclasts (the cells that break down bone). The denosumab development program is the largest ever initiated by Amgen. This broad and deep development program demonstrates Amgen's commitment to researching and delivering pioneering medicines to patients with unmet medical needs. Amgen is studying denosumab in numerous tumor types across the spectrum of cancer-related bone diseases. Over 11,000 patients have been enrolled in the denosumab oncology clinical trials, testing the drug for the reduction of SREs in patients with breast and prostate cancer, as well as other solid tumors and multiple myeloma, for the amelioration of treatment-induced bone loss in patients with non-metastatic breast or prostate cancers, and for its potential to delay bone metastases in prostate and breast cancers.

## **About Amgen**

Amgen discovers, develops, manufactures and delivers innovative human therapeutics. A biotechnology pioneer since 1980, Amgen was one of the first companies to realize the new science's promise by bringing safe and effective medicines from lab, to manufacturing plant, to patient. Amgen therapeutics have changed the practice of medicine, helping millions of people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, and other serious illnesses. With a deep and broad pipeline of potential new medicines, Amgen remains committed to advancing science to dramatically improve people's lives. To learn more about our pioneering science and our vital medicines, visit [www.amgen.com](http://www.amgen.com).

## **Forward-Looking Statements**

This news release contains forward-looking statements that are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described. 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 (SEC) reports filed by Amgen, including Amgen's most recent annual report on Form 10-K and most recent periodic reports on Form 10-Q and Form 8-K. Please refer to Amgen's most recent Forms 10-K, 10-Q and 8-K for additional information on the uncertainties and risk factors related to our business. Unless otherwise noted, Amgen is providing this information as of Oct. 10, 2010 and expressly disclaims any duty to update information contained in this news release.

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. 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 business may be impacted by government investigations, litigation and products liability claims. We depend on third parties for a significant portion of our manufacturing capacity for the supply of certain of our current and future products and limits on supply may constrain sales of certain of our current products and product candidate development.

In addition, sales of our products are affected by the reimbursement policies imposed by third-party payors, 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 health care cost containment as well as U.S. legislation affecting pharmaceutical pricing and reimbursement. Government and others' regulations and reimbursement policies may affect the development, usage and pricing of our products. In addition, we compete with other companies with respect to some of our marketed products as well as for the discovery and development of new products. We believe that some of our newer products, product candidates or new indications for existing products, may face competition when and as they are approved and marketed. Our products may compete against products that have lower prices, established reimbursement, superior performance, are easier to administer, or that are otherwise competitive with our products. In addition, 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 and there can be no guarantee of our ability to obtain or maintain patent protection for our products or product candidates. We cannot guarantee that we will be able to produce commercially successful products or maintain the commercial success of our existing products. Our stock price may be affected by actual or perceived market opportunity, competitive position, and success or failure of our products or product candidates. Further, 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.

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 (FDA) for the products. The products are not approved for their 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. Only

the FDA can determine whether the products are safe and effective for these uses. Healthcare professionals should refer to and rely upon the FDA-approved labeling for the products, and not the information discussed in this news release.

**Editor's Note:** Denosumab administered as a 60 mg single subcutaneous injection every six months has been approved under the trade name Prolia(TM) in the United States for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Prolia has also been approved in the EU to treat osteoporosis in postmenopausal women at increased risk of fracture and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. The Prolia trade name may not apply for future indications of denosumab. For full Prolia prescribing information, please visit [www.prolia.com](http://www.prolia.com).

Denosumab is currently under global regulatory review for the reduction of SREs in patients with advanced cancer. The advanced cancer program is evaluating 120 mg/kg denosumab administered as a monthly subcutaneous injection.

- (i) Cleeland CS, et al. Pain and its treatment in outpatients with metastatic cancer. *N Eng J Med*. 1994; 330:592-596.
- (ii) Coleman RE. Skeletal complications of malignancy. *Cancer*. 1997; 80(suppl): 1588-1594.
- (iii) Lipton A, Theriault RL, Hortobagyi GN. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases. *Cancer* 2000;88:1082-1090.
- (iv) Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlated with reduced survival in patients with malignant bone disease. *Cancer*. 2007;110:1860-1867.
- (v) Rosen LS, Gordon D, Tchekmedyian NS, et al. Nonsmall cell lung carcinoma and other solid tumors. *Cancer*. 2004;100:2613-2621.
- (vi) Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer*. 2008; 16: 879-889.
- (vii) Norgaard M, Jensen AO, Jacobsen JB, Cetin K, Fryzek JP, Sorensen HT. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol* 2010; 184:162-167.
- (viii) Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726-1733.
- (ix) Saad F, Gleason DM, Murray R, et al. A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma. *Journal Ntl Cancer Inst* 2002;19:1458-1468.
- (x) Delea T, Langer C, McKiernan J, et al. The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer. *Oncology* 2004;67:390-396.
- (xi) Schulman KL, Kohles J. Economic burden of metastatic bone disease in the U.S. *American Cancer Society* 2007:2334-2342.
- (xii) GVD/2007:2334-2342. Barber ISPOR 2008 Poster
- (xiii) Lage MJ, Barber BL, Harrison DJ, Jun S. The Cost of Treating Skeletal-Related Events in Patients With Prostate Cancer. *Am J Manag Care*. 2008;14:317-322
- (xiv) Schulman KL, Kohles J. Economic burden of metastatic bone disease in the U.S. *American Cancer Society* 2007:2334-2342.

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