Study Results Published in the Journal of the American Medical Association Show Amgen's Parsabiv™ (Etelcalcetide) Significantly Reduced Serum Parathyroid Hormone in Adults With Secondary Hyperparathyroidism on Hemodialysis

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THOUSAND OAKS, Calif., Jan. 10, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced the *Journal of the American Medical Association* (*JAMA*) publication of findings from three Phase 3 studies of Parsabiv™ (etelcalcetide), an investigational intravenous calcimimetic agent in the U.S. The studies evaluated Parsabiv in more than 1,700 adults with secondary hyperparathyroidism (sHPT) on hemodialysis and showed that the drug produced statistically significant and clinically meaningful reductions in serum parathyroid hormone (PTH) levels, a key marker of sHPT. sHPT is a chronic and serious condition that is often progressive among patients with chronic kidney disease (CKD) and is associated with significant clinical consequences.[1]

"sHPT is often a progressive condition in patients with advanced chronic kidney disease, including those with kidney failure. Despite the use of phosphate binders and calcitriol or active vitamin D analogs, management of sHPT has been relatively poor in a sizeable proportion of patients," said Glenn M. Chertow, M.D., professor of Medicine and chief of the Division of Nephrology at Stanford University School of Medicine. "Intravenous treatment with etelcalcetide could give healthcare providers greater control over calcimimetic delivery, and provide patients with sHPT on hemodialysis an additional treatment option, lowering parathyroid hormone and improving other key laboratory parameters."

In two parallel Phase 3 randomized placebo-controlled studies in CKD patients with sHPT on hemodialysis, Parsabiv met the primary endpoint and significantly reduced serum PTH by more than 30 percent in 74.7 percent of patients compared to 8.9 percent given placebo. In addition, a head-to-head study comparing Parsabiv to oral Sensipar® (cinacalcet) also met its primary endpoint. This head-to-head study showed Parsabiv was non-inferior to oral Sensipar in the proportion of patients achieving 30 percent or greater serum PTH reduction. Further, Parsabiv was superior to Sensipar for the secondary endpoints of proportion of patients achieving greater than 30 percent and greater than 50 percent reduction in mean PTH during the Efficacy Assessment Phase (EAP) compared with baseline.

A total of 1,706 patients were enrolled across the three trials to evaluate the safety and efficacy of Parsabiv in the treatment of adult sHPT patients on hemodialysis.

The two placebo-controlled trials were double-blind studies in a total of 1,023 adult patients with sHPT on hemodialysis. The patients were randomized to receive intravenous Parsabiv or placebo three times a week at the end of their dialysis sessions, and both arms also received standard of care as prescribed by the treating physician. Both of the trials showed that, by weeks 20-27, significantly more Parsabiv patients compared to placebo patients achieved:

- Greater than a 30 percent reduction from baseline in mean serum PTH during weeks 20-27: 74.0 percent versus 8.3 percent (p<0.001) and 75.3 percent versus 9.6 percent (p<0.001)
- Serum PTH levels of 300 pg/mL or less: 49.6 percent versus 5.1 percent (p<0.001) and 53.3 percent versus 4.6 percent (p<0.001)

The most common treatment-emergent adverse events (TEAEs) in the placebo-controlled studies that occurred at a rate greater than 10 percent in the Parsabiv group, and more frequently than in the placebo group in either of the studies, were blood calcium decreases (asymptomatic reductions in serum calcium), muscle spasms, diarrhea, nausea and vomiting. The overall rates of fatal adverse events, serious adverse events and adverse events leading to discontinuation of investigational product were similar in the Parsabiv and placebo groups.

The head-to-head study against Sensipar included 683 patients with sHPT on hemodialysis, and found Parsabiv resulted in a higher proportion of patients reaching at least a 30 percent reduction in mean serum PTH during weeks 20-27 compared to baseline: 68.2 percent versus 57.7 percent, respectively (p=0.004). Significantly more Parsabiv patients also achieved greater than a 50 percent reduction from baseline in mean serum PTH during weeks 20-27: 52.4 percent versus 40.2 percent, respectively (p=0.001). There was no statistically significant difference between the two groups in the mean number of days of vomiting or nausea per week in the first eight weeks, a secondary endpoint. TEAEs that were reported in greater than 10 percent of patients in either arm included blood calcium decreases, nausea, vomiting and diarrhea. TEAEs of hypocalcemia (symptomatic) were reported in 5.0 percent of patients who received Parsabiv versus 2.3 percent in the Sensipar group.

"As we work toward advancing the treatment of patients with sHPT on hemodialysis, the findings published in *JAMA* are particularly noteworthy given patients were typically receiving conventional therapy for sHPT, but showed a sustained reduction in PTH over 26 weeks in the placebo controlled trials," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "We are encouraged by these data as they demonstrate improvements in key biomarkers for sHPT and support its potential for a disease that has not seen any advances in more than a decade."

In the U.S., the Parsabiv application has been resubmitted to the Food and Drug Administration (FDA) addressing the Complete Response Letter. The U.S. user fee goal date is Feb. 9, 2017. On Nov. 11, 2016, the European Commission (EC) granted marketing authorization for Parsabiv for the treatment of sHPT in adult patients with CKD on hemodialysis. Russian regulatory authorities approved Parsabiv on Dec. 5, 2016. Regulatory submissions for Parsabiv are currently pending in Colombia, Brazil, Switzerland and South Africa. On Dec. 19, 2016, Amgen's collaborator, Ono Pharmaceuticals, received manufacturing and marketing approval in Japan for Parsabiv for the treatment of secondary hyperparathyroidism in patients on hemodialysis.

About the Phase 3 Placebo-Controlled Studies
In the two 26-week, multicenter, randomized, double-blind, placebo-controlled studies, an aggregate of 1,023 adult patients with sHPT (PTH greater than 400 pg/mL) on hemodialysis were randomized to receive intravenous Parsabiv or placebo three times a week at the end of their dialysis sessions. All patients, regardless of treatment assignment, received standard of care with phosphate binders and calcitriol or active vitamin D analogs, as

prescribed.

The primary endpoint of the studies was the proportion of patients achieving greater than 30 percent reduction in PTH during the EAP. Secondary endpoints included the proportion of patients with PTH less than or equal to 300 pg/mL during the EAP, and percent change from baseline during the EAP for PTH, serum calcium, phosphate and calcium phosphate product (Ca x P).

About the Phase 3 Head-to-Head Study
The Phase 3 randomized, double-blind, double-dummy, active controlled trial was designed to compare the efficacy and safety of intravenous Parsabiv and oral Sensipar in 683 adult sHPT patients (340 randomized to Parsabiv and 343 to Sensipar) on hemodialysis. The patients were from 164 sites in the U.S., Canada, Europe, Russia and New Zealand. Patients receiving maintenance hemodialysis three times per week with sHPT (pre-dialysis serum PTH>500 pg/mL) on stable doses of calcium supplements or phosphate binders and calcitriol or active vitamin D analogs, if prescribed, with albumin-corrected serum calcium ≥8.3 mg/dL were eligible for participation.

Patients who were randomized to treatment with Parsabiv/oral placebo received intravenous doses three times a week at the end of their dialysis sessions and daily oral doses of placebo tablets. Patients in the comparison group received daily oral doses of Sensipar tablets and intravenous doses of placebo three times a week at the end of their dialysis sessions. The primary endpoint was the proportion of patients with greater than 30 percent reduction from baseline in mean serum PTH during the EAP (weeks 20-27). Key secondary endpoints included the proportion of patients with greater than 50 percent and greater than 30 percent reduction in PTH, and the mean weekly days of self-reported nausea and vomiting over the first eight weeks.

About Secondary Hyperparathyroidism
sHPT is a chronic and serious condition which affects many of the approximately two million people throughout the world who are receiving dialysis, including 468,000 people in the U.S.[1-3] Approximately 88 percent of dialysis patients and 79 percent of patients on hemodialysis will develop sHPT.[4] sHPT refers to the excessive secretion of PTH by the parathyroid glands in response to decreased renal function and impaired mineral metabolism.[1,5] The elevated levels of PTH can lead to an increase in the release of calcium and phosphorus from the bones.[6] sHPT is often initially silent and asymptomatic.[1] As a result, sHPT is frequently underdiagnosed and undertreated.[1,7]

About Parsabiv™ (etelcalcetide) in the U.S.
Parsabiv is a novel calcimimetic agent in clinical development for the treatment of sHPT in adult CKD patients on hemodialysis that is administered intravenously at the end of the hemodialysis session. A calcimimetic is a drug that mimics the action of calcium by activating the calcium-sensing receptors on the parathyroid gland. Parsabiv binds to and activates the calcium-sensing receptor on the parathyroid gland, thereby decreasing PTH levels.

Parsabiv Indication and Important Safety Information in the EU
Parsabiv is indicated for the treatment of secondary hyperparathyroidism (sHPT) in adult patients with chronic kidney disease (CKD) on hemodialysis therapy.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Parsabiv should not be initiated if corrected serum calcium is less than the lower limit of the normal range.

Special Warnings and Precautions:
Hypocalcaemia: Since Parsabiv lowers serum calcium, patients should be advised to seek medical attention if they experience symptoms of hypocalcaemia and should be monitored for the occurrence of hypocalcaemia. Serum calcium levels should be measured prior to initiating treatment, within 1 week of initiation or dose adjustment of Parsabiv and every 4 weeks during treatment. Potential manifestations of hypocalcaemia include paraesthesias, myalgias, muscle spasm and seizures. Decreases in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia. The threshold for seizures may be lowered by significant reductions in serum calcium levels.

Worsening heart failure: Decreased myocardial performance, hypotension, and congestive heart failure may be associated with significant reductions in serum calcium levels.

Co-administration with other medicinal products

Administer Parsabiv with caution in patients receiving any other medicinal products known to lower serum calcium. Patients receiving Parsabiv should not be given cinacalcet. Concurrent administration may result in severe hypocalcaemia.

Interactions: No interaction studies have been performed. There is no known risk of pharmacokinetic interaction with Parsabiv.

Fertility, Pregnancy and Lactation: There are no or limited amount of data from the use of Parsabiv in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Parsabiv during pregnancy. A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Parsabiv therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No data are available on the effect of Parsabiv on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Undesirable Effects: The following common (≥10%) adverse reactions have been reported in pivotal, controlled clinical studies: decreases in serum calcium, diarrhea, nausea, vomiting, and muscle spasms.

Pharmaceutical Precautions: Store in a refrigerator (2 degrees C – 8 degrees C). Once removed from the refrigerator, Parsabiv must be used within 7 days if stored in the original carton.

To see the full Parsabiv Safety Information, visit http://www.ema.europa.eu.

About Sensipar® (cinacalcet) in the U.S.
Sensipar® (cinacalcet) is the first oral calcimimetic agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of sHPT in adult patients with CKD on dialysis. Sensipar is not indicated for use in adult patients with CKD who are not on dialysis because of an increased risk of hypocalcemia. The therapy is also approved in the U.S. for treatment of hypercalcemia in adult patients with parathyroid carcinoma and hypercalcemia

in adult patients with primary hyperparathyrodisim (HPT) for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy. Sensipar binds to the calcium-sensing receptor, resulting in a drop in PTH levels by inhibiting PTH synthesis and secretion. In addition, the reductions in PTH lower serum calcium and phosphorus levels.

Sensipar Important Safety Information in the U.S.
Sensipar® (cinacalcet) treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range (8.4 mg/dL).

Sensipar® lowers serum calcium; therefore, it is important that patients are carefully monitored for the occurrence of hypocalcemia. Life threatening events and fatal outcomes associated with hypocalcemia have been reported in patients treated with Sensipar®, including pediatric patients. Decreases in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcemia have been reported in patients treated with Sensipar®.

Significant reductions in calcium may lower the threshold for seizures. Patients, particularly those with a history of seizure disorder, should be carefully monitored for the occurrence of low serum calcium or symptoms of hypocalcemia.

In Sensipar® postmarketing use, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia were reported in patients with impaired cardiac function. The causal relationship to Sensipar® therapy could not be completely excluded and may be mediated by reductions in serum calcium levels.

Adynamic bone disease may develop if intact parathyroid hormone (iPTH) levels are suppressed below 100 pg/mL. Patients with moderate to severe hepatic impairment should be monitored throughout treatment with Sensipar®, as cinacalcet exposure assessed by area under the curve (AUC) was higher than in patients with normal hepatic function.

Patients with secondary HPT: Serum calcium and serum phosphorus should be measured within 1 week and PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Sensipar®. Once the maintenance dose has been established, serum calcium and serum phosphorus should be measured approximately monthly, and PTH every 1 to 3 months. Patients with primary HPT or parathyroid carcinoma: Serum calcium should be measured within 1 week after initiation or dose adjustment of Sensipar®. Once maintenance dose levels have been established, serum calcium should be measured every 2 months.

In clinical trials of patients with secondary HPT comparing Sensipar® to placebo, the most commonly reported side effects were nausea (31 percent vs. 19 percent), vomiting (27 percent vs. 15 percent), and diarrhea (21 percent vs. 20 percent). In clinical trials of patients with primary HPT and parathyroid carcinoma treated with Sensipar®, the most commonly reported side effects were nausea (63 percent), vomiting (46 percent), and paresthesia (20 percent).

Please see Full Prescribing Information.

About Mimpara® (cinacalcet) in the EU
Mimpara® (cinacalcet) is the first oral calcimimetic agent approved by the European Medicines Agency for the treatment of sHPT in patients with CKD on dialysis. The therapy is also approved in the EU for the treatment of hypercalcemia in patients with parathyroid carcinoma and hypercalcemia in adult patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated. Mimpara binds to the calcium-sensing receptor, resulting in a drop in PTH levels by inhibiting PTH synthesis and secretion. In addition, the reductions in PTH lower serum calcium and phosphorus levels.

Mimpara Important Safety Information in the EU
Contraindications: Hypersensitivity to the active substance or to any of the excipients

Special Warnings and Precautions:
Serum Calcium:

Mimpara treatment should not be initiated in patients with a serum calcium below the lower limit of the normal range. Life threatening events and fatal outcomes associated with hypocalcaemia have been reported in adult and paediatric patients treated with Mimpara. Manifestations of hypocalcaemia may include paraesthesias, myalgias, cramping, tetany and convulsions. Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia secondary to hypocalcaemia. The threshold for seizures is lowered by significant reductions in serum calcium levels. Patients should be monitored carefully for the occurrence of hypocalcaemia. Serum calcium should be measured within 1 week after initiation or dose adjustment of Mimpara. Once the maintenance dose has been established, serum calcium should be measured approximately monthly.

Hypotension and/or worsening heart failure: In post-marketing safety surveillance, isolated, idiosyncratic cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels.

Hepatic impairment:

Due to the potential for 2 to 4 fold higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment, Mimpara should be used with caution in these patients and treatment should be closely monitored.

In the treatment of secondary hyperparathyroidism the most commonly reported adverse reactions in clinical trials were nausea and vomiting.

To see the full Mimpara Safety Information, visit http://www.ema.europa.eu.

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 and follow us on 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. 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 related to our product candidates is preliminary and investigative. Such product candidates are not approved by the U.S. Food and Drug Administration, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates.

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