The Lancet Publishes Results From COSMIC-HF Trial Showing Omecamtiv Mecarbil Significantly Improved Cardiac Function In Patients With Chronic Heart Failure

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THOUSAND OAKS, Calif. and SOUTH SAN FRANCISCO, Calif., Nov. 30, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and Cytokinetics, Inc. (NASDAQ:CYTK) today announced *The Lancet* published results from a Phase 2 clinical trial evaluating omecamtiv mecarbil in patients with chronic heart failure. The COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial met its primary pharmacokinetic objective and showed statistically significant improvements in all pre-specified secondary measures of cardiac function in the treatment group receiving pharmacokinetic-based dose titration. The results were initially presented as a Late-Breaking Clinical Trial at the American Heart Association (AHA) Scientific Sessions 2015.[1]

"Data from COSMIC-HF underscore the potential of omecamtiv mecarbil for the treatment of chronic heart failure, a disease that remains a growing healthcare problem worldwide," said John Teerlink, M.D., professor of Clinical Medicine at the University of California, San Francisco and director of Heart Failure at the San Francisco Veterans Affairs Medical Center. "The findings from COSMIC-HF support the therapeutic hypothesis that directly improving cardiac systolic function with a cardiac myosin activator may reverse abnormal structural changes and neurohormonal activation associated with the progression of heart failure."

The trial, which evaluated 448 patients with chronic heart failure and left ventricular systolic dysfunction, showed that dose titration controlled patient exposure to omecamtiv mecarbil. Patients were randomized 1:1:1 to receive either placebo or treatment with omecamtiv mecarbil dosed as 25 mg twice daily or 25 mg with dose escalation to 50 mg twice daily, depending on plasma concentrations of omecamtiv mecarbil after two weeks of treatment.

The pharmacokinetic-based dose titration strategy was designed to maintain patient exposure to omecamtiv mecarbil in the targeted plasma concentration range. Approximately 53 percent of patients in the dose titration group were escalated to a dose of 50 mg twice daily.

Following 20 weeks of treatment, statistically significant improvements were observed in all pre-specified secondary endpoint measures of cardiac function in the dose titration group, compared to placebo. Systolic ejection time increased by 25.0 msec (p<0.0001), stroke volume increased by 3.6 mL (p=0.0217) and heart rate decreased by 3.0 beats per min (p=0.0070). Left ventricular end-systolic and end-diastolic dimensions decreased by 1.8 mm (p=0.0027) and 1.3 mm (p=0.0128), respectively, and were associated with statistically significant reductions in left ventricular end-systolic and end-diastolic volumes. N-terminal pro-brain natriuretic peptide (NT-proBNP) decreased by 970 pg/mL (p=0.0069). In pre-specified exploratory analyses of the dose titration group, placebo-corrected reductions in NT-proBNP persisted four weeks after stopping omecamtiv mecarbil, decreasing further to 1,306 pg/mL (p=0.0006). The data also showed increases in fractional shortening at week 20 compared to placebo in the dose titration group.

"The mechanism of action for omecamtiv mecarbil is novel, and these data reinforce its potential as a new therapy for the millions of patients living with heart failure around the world," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "In collaboration with our partners Cytokinetics and Servier, we look forward to initiating our Phase 3 clinical trial program for omecamtiv mecarbil where we will learn if the improvements in cardiac function observed in the COSMIC-HF study translate into improved cardiovascular outcomes for patients."

"Results from COSMIC-HF provide further validation for the pharmacodynamic effects of omecamtiv mecarbil and show its potential to reverse ventricular enlargement in patients living with chronic heart failure," said Robert I. Blum, president and CEO at Cytokinetics. "We look forward to advancing omecamtiv mecarbil into its Phase 3 program designed to investigate correlations between cardiac function and clinical outcomes."

Adverse events (AEs), including serious AEs, in patients on omecamtiv mecarbil were comparable to placebo. The incidence of adjudicated deaths (3 percent died on placebo, 1 percent died on omecamtiv mecarbil 25 mg twice daily, 2 percent died on omecamtiv mecarbil dose titration), myocardial infarction (1 percent on placebo, 0 percent on omecamtiv mecarbil 25 mg twice daily, 1 percent on omecamtiv mecarbil dose titration) and unstable angina (0 percent on placebo, 1 percent on omecamtiv mecarbil 25 mg twice daily, 0 percent on omecamtiv mecarbil dose titration) was similar. Other cardiac AEs were generally balanced between placebo and active treatment groups. In patients receiving omecamtiv mecarbil compared to placebo, cardiac troponin increased by 0.001 ng/mL and 0.006 ng/mL (median change from baseline at week 20) in the 25 mg twice daily group and dose titration group, respectively. Events of increased troponin (n=278 across all treatment groups) were independently adjudicated and none were adjudicated as an episode of myocardial ischemia or infarction.

About Heart Failure

Heart failure is a grievous condition that affects more than 23 million people worldwide,[2,3] about half of whom have reduced left ventricular function.[4,5] It is the leading cause of hospitalization and readmission in people age 65 and older.[6,7] Despite broad use of standard treatments and advances in care, the prognosis for patients with heart failure is poor.[8] An estimated one in five people over the age of 40 are at risk of developing heart failure, and approximately 50 percent of people diagnosed with heart failure will die within five years of initial hospitalization.[9,10]

COSMIC-HF Trial Design

COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) was a double-blind, randomized, placebo-controlled, multicenter, Phase 2 trial designed to evaluate an oral formulation of omecamtiv mecarbil in chronic heart failure patients with reduced ejection fraction. The trial consisted of two parts, a dose escalation phase and a larger and longer expansion phase. The dose escalation phase, which completed in 2013, assessed the pharmacokinetics and tolerability of three oral modified-release formulations of omecamtiv mecarbil and was used to select one formulation for further evaluation in the expansion phase. In the dose escalation phase, 96 patients were randomized 1:1:1:1 to placebo or one of three oral modified-release formulations of omecamtiv mecarbil in two cohorts (25 mg twice daily or 50 mg twice daily). Each patient cohort was followed for 35 days.

The expansion phase evaluated 448 chronic heart failure patients with reduced ejection fraction who were dosed with the selected oral formulation of

omecamtiv mecarbil for 20 weeks and followed for a total of 24 weeks. Patients were randomized 1:1:1 to receive either placebo or treatment with omecamtiv mecarbil 25 mg twice daily or 25 mg with dose escalation to 50 mg twice daily, depending on plasma concentrations of omecamtiv mecarbil after two weeks of treatment. The pharmacokinetic-based dose titration strategy was designed to maintain patient exposure to omecamtiv mecarbil in a targeted plasma concentration range; approximately 53 percent of patients in the dose titration group were escalated to a dose of 50 mg twice daily.

The primary endpoints for the expansion phase were to assess the maximum and pre-dose plasma concentration of omecamtiv mecarbil. The secondary endpoints were to assess changes from baseline in systolic ejection time, stroke volume, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, heart rate and NT-proBNP (a biomarker associated with the severity of heart failure) at week 20, as well as the safety and tolerability of omecamtiv mecarbil including incidence of adverse events from baseline to week 24.

COSMIC-HF was not designed to assess the impact of omecamtiv mecarbil on cardiovascular outcomes in heart failure patients.

COSMIC-HF was conducted by Amgen in collaboration with Cytokinetics.

About Omecamtiv Mecarbil
Omecamtiv mecarbil is a novel cardiac myosin activator. Cardiac myosin is the cytoskeletal motor protein in the cardiac muscle cell that is directly responsible for converting chemical energy into the mechanical force resulting in cardiac contraction. Cardiac myosin activators are thought to accelerate the rate-limiting step of the myosin enzymatic cycle and shift the enzymatic cycle in favor of the force-producing state. Preclinical research has shown that cardiac myosin activators increase contractility in the absence of changes in intracellular calcium in cardiac myocytes.[11-13]

Omecamtiv mecarbil is being developed by Amgen in collaboration with Cytokinetics. Amgen holds an exclusive, worldwide license to omecamtiv mecarbil and related compounds, subject to Cytokinetics' specified development and commercialization rights. Servier has exercised an exclusive option granted by Amgen for the commercialization of omecamtiv mecarbil in Europe, as well as the Commonwealth of Independent States, including Russia.

About Amgen Cardiovascular
Building on more than three decades of experience in developing biotechnology medicines for patients with serious illnesses, Amgen is dedicated to addressing important scientific questions to advance care and improve the lives of patients with cardiovascular disease, the leading cause of morbidity and mortality worldwide.[14] Amgen's research into cardiovascular disease, and potential treatment options, is part of a growing competency at Amgen that utilizes human genetics to identify and validate certain drug targets. Through its own research and development efforts, as well as partnerships, Amgen is building a robust cardiovascular portfolio consisting of several approved and investigational molecules in an effort to address a number of today's important unmet patient needs, such as high cholesterol and heart failure.

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.

About Cytokinetics
Cytokinetics is a late-stage biopharmaceutical company focused on discovering, developing and commercializing first-in-class muscle activators as potential treatments for debilitating diseases in which muscle performance is compromised and/or declining. As a leader in muscle biology and the mechanics of muscle performance, the company is developing small molecule drug candidates specifically engineered to increase muscle function and contractility. Cytokinetics' lead drug candidate is *tirasemtiv*, a fast skeletal muscle troponin activator, for the potential treatment of ALS. *Tirasemtiv* has been granted orphan drug designation and fast track status by the U.S. Food and Drug Administration and orphan medicinal product designation by the European Medicines Agency for the potential treatment of ALS. Cytokinetics retains the right to develop and commercialize *tirasemtiv*, subject to an option held by Astellas Pharma Inc. Cytokinetics is also collaborating with Astellas to develop CK-2127107, a fast skeletal muscle activator, for the potential treatment of spinal muscular atrophy, chronic obstructive pulmonary disease and ALS. Cytokinetics is collaborating with Amgen Inc. to develop *omecamtiv mecarbil*, a novel cardiac muscle activator, for the potential treatment of heart failure. Amgen holds an exclusive license worldwide to develop and commercialize *omecamtiv mecarbil* and Astellas holds an exclusive license worldwide to develop and commercialize CK-2127107. Both licenses are subject to Cytokinetics' specified development and commercialization participation rights. For additional information about Cytokinetics, visit http://www.cytokinetics.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 or European Commission, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates.

Cytokinetics Forward-Looking Statements
This press release contains forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"). Cytokinetics disclaims any intent or obligation to update these forward-looking statements, and claims the protection of the Act's Safe Harbor for forward-looking statements. Examples of such statements include, but are not limited to, statements relating to Cytokinetics' and its partners' research and development activities, including the significance and utility of COSMIC-HF clinical trial results and the potential progression of *omecamtiv mecarbil* to Phase 3 development; and the properties and potential benefits of Cytokinetics' drug candidates. Such statements are based on management's current expectations, but actual results may differ materially due to various risks and uncertainties, including, but not limited to Amgen's decisions with respect to the design, initiation, conduct, timing and continuation of development activities for *omecamtiv mecarbil*; potential difficulties or delays in the development, testing, regulatory approvals for trial commencement, progression or product sale or manufacturing, or production of Cytokinetics' drug candidates that could slow or prevent clinical development or product approval, including risks that current and past results of clinical trials or preclinical studies may not be indicative of future clinical trials results, patient enrollment for or conduct of clinical trials may be difficult or delayed, Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy, the U.S. Food and Drug Administration or foreign regulatory agencies may delay or limit Cytokinetics' or its partners' ability to conduct clinical trials, and Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Cytokinetics may incur unanticipated research and development and other costs or be unable to obtain additional financing necessary to conduct development of its products; standards of care may change, rendering Cytokinetics' drug candidates obsolete; competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target; and risks and uncertainties relating to the timing and receipt of payments from its partners, including milestones and royalties on future potential product sales under Cytokinetics' collaboration agreements with such partners. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission. Forward-looking statements are not guarantees of future performance, and Cytokinetics' actual results of operations, financial condition and liquidity, and the development of the industry in which it operates, may differ materially from the forward-looking statements contained in this press release. Any forward-looking statements that Cytokinetics makes in this press release speak only as of the date of this press release. Cytokinetics assumes no obligation to update its forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

CONTACT: Amgen, Thousand Oaks
Kristen Davis, 805-447-3008 (media)
Kristen Neese, 805-313-8267 (media)
Arvind Sood, 805-447-1060 (investors)

CONTACT: Cytokinetics, South San Francisco
Diane Weiser, 415-290-7757 (investors and media)

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