Cytokinetics Announces Preclinical Data for CK-3773274 Presented at the Biophysical Society 64th Annual Meeting

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Preclinical Studies Demonstrate Distinct Binding Site for Next-Generation Cardiac Myosin Inhibitor

SOUTH SAN FRANCISCO, Calif., Feb. 20, 2020 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that preclinical data related to CK-3773274 (CK-274) were presented at the Biophysical Society 64th Annual Meeting in San Diego, CA elaborating on its mechanism of action and properties to modulate cardiac contractility *in vitro* and *in vivo*. CK-274 is a next-generation cardiac myosin inhibitor discovered by company scientists, in development for the potential treatment of hypertrophic cardiomyopathy (HCM).

"These data further characterize how CK-274 decreases cardiac contractility *in vitro* and *in vivo*, and provide evidence for a distinct and selective mechanistic binding site for CK-274 on cardiac myosin," said Brad Morgan, Ph.D., Cytokinetics' Senior Vice President, Research and Non-Clinical Development. "We are pleased to contribute these preclinical data supporting translation of cardiac myosin inhibition as a novel approach to the potential treatment of diseases associated with hypercontractility as we conduct REDWOOD-HCM, the Phase 2 clinical trial of CK-274 in patients with obstructive hypertrophic cardiomyopathy."

Preclinical Research Data Presented at Biophysical Society Annual Meeting

Previous *in vitro* and *in vivo* studies have shown that CK-274 reduced cardiac contractility and reduced fractional shortening (a measure of cardiac function) in a dose and concentration dependent manner. New data presented at the Biophysical Society Annual Meeting demonstrate that CK-274 reduces cardiac myosin activity *in vitro*, and importantly it does not inhibit the actin-activated ATPase activity of smooth muscle myosin, supportive of its selectivity for cardiac myosin. Transient kinetic studies also show that CK-274 slows the rate of actin-activated phosphate release, without affecting ATP binding and hydrolysis, consistent with a mechanism that stabilizes myosin in weak actin-binding conformations. Additionally, the binding of CK-274 to cardiac myosin is shown to be mutually exclusive with the non-selective myosin inhibitor *blebbistatin*, thus suggesting they bind to the same or overlapping locations on cardiac myosin, but distinctly from one another given the differences in their selectivity for cardiac myosin. In contrast, the binding of *blebbistatin* and *mavacamten,* a cardiac myosin inhibitor, are not mutually exclusive, indicating CK-274 and *mavacamten* have distinct binding sites on cardiac myosin. These data characterize how CK-274 reduces cardiac contractility and demonstrate that cardiac myosin inhibition may address the underlying hypercontractility of the sarcomere in hypertrophic cardiomyopathies.

About CK-274

CK-274 is a novel, oral, small molecule cardiac myosin inhibitor that company scientists discovered independent of its collaborations. CK-274 arose from an extensive chemical optimization program conducted with careful attention to therapeutic index and pharmacokinetic properties that may translate into next-in-class potential in clinical development. CK-274 was designed to reduce the hypercontractility that is associated with hypertrophic cardiomyopathy (HCM). In preclinical models, CK-274 reduces myocardial contractility by binding directly to cardiac myosin at a distinct and selective allosteric binding site, thereby preventing myosin from entering a force producing state. CK-274 reduces the number of active actin-myosin cross bridges during each cardiac cycle and consequently reduces myocardial contractility. This mechanism of action may be therapeutically effective in conditions characterized by excessive hypercontractility, such as HCM.

In preclinical models of cardiac function, both in normal models of cardiac function and mouse models of HCM, CK-274 reduced cardiac contractility in a predictable dose and exposure dependent fashion. The preclinical pharmacokinetics of CK-274 were characterized, evaluated and optimized for potential ease-of-use in the clinical setting. A Phase 1 study demonstrated that CK-274 was safe and well tolerated in healthy participants. The pharmacokinetics of CK-274 were generally dose linear, and steady-state appeared evident within 14 days of dosing. Left ventricular ejection fraction decreased in an exposure dependent manner and the PK/PD relationship for CK-274 observed in humans was similar to that observed preclinically when adjusted for differences in protein binding. Specifically, the shallow exposure-response relationship observed preclinically appears to translate to humans and may enable flexible dose optimization in humans.

The overall development program will assess the potential of CK-274 to improve exercise capacity and relieve symptoms in patients with hyperdynamic ventricular contraction due to HCM.

About Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an inherited cardiovascular disorder in which the heart muscle (myocardium) becomes abnormally thick (hypertrophied). The thickening of cardiac muscle leads to the inside of the left ventricle becoming smaller and stiffer, and thus the ventricle becomes less able to relax and fill with blood. In the majority of patients, thickening of the heart muscle in the left ventricular outflow tract obstructs the flow of blood out of the heart. This ultimately limits the heart's pumping function, resulting in symptoms including chest pain, dizziness, shortness of breath, or fainting during physical activity. A subset of patients with HCM are at high risk of progressive disease which can lead to ventricular arrhythmias, atrial fibrillation, stroke, heart failure and sudden cardiac death. There are no current medical treatments that directly address the hypercontractility that underlies HCM.

About Cytokinetics

Cytokinetics is a late-stage biopharmaceutical company focused on discovering, developing and commercializing first-in-class muscle activators and next-in-class muscle inhibitors 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 impact muscle function and contractility. Cytokinetics is collaborating with Amgen Inc. (Amgen) to develop *omecamtiv mecarbil*, a novel cardiac muscle activator. *Omecamtiv mecarbil* is the subject of an international clinical trials program in patients with heart failure including GALACTIC-HF and METEORIC-HF. Amgen holds an exclusive worldwide license to develop and commercialize *omecamtiv mecarbil* with a sublicense held by Servier for commercialization in Europe and certain other countries. Cytokinetics is collaborating with Astellas Pharma Inc. (Astellas) to develop *reldesemtiv*, a fast skeletal muscle troponin activator (FSTA). Astellas currently holds an exclusive worldwide license to develop and commercialize *reldesemtiv*. Licenses held by Amgen and Astellas are subject to specified co-development and co-commercialization rights of

Cytokinetics. Cytokinetics is also developing CK-274, a novel cardiac myosin inhibitor that company scientists discovered independent of its collaborations, for the potential treatment of hypertrophic cardiomyopathies. Cytokinetics continues its over 20-year history of pioneering innovation in muscle biology and related pharmacology focused to diseases of muscle dysfunction and conditions of muscle weakness.

For additional information about Cytokinetics, visit www.cytokinetics.com and follow us on Twitter, LinkedIn, Facebook and YouTube.

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 the timing, design and results of Cytokinetics' Phase 1 clinical trial of CK-274; the potential benefits of CK-274; Cytokinetics' and its partners' research and development activities; the timing of enrollment of patients in Cytokinetics' and its partners' clinical trials; the design, timing, results, significance and utility of preclinical and clinical results; 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, 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; 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 FDA or foreign regulatory agencies may delay or limit Cytokinetics' or its partners' ability to conduct clinical trials; Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Cytokinetics' partners decisions with respect to research and development activities; 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.

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References

[1] Planelles-Herrero VJ, Hartman JJ, Robert-Paganin J. et al. Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil. *Nat Commun*. 2017;8:190.

[2] Shen YT, Malik FI, Zhao X, et al. Improvement of cardiac function by a cardiac myosin activator in conscious dogs with systolic heart failure. *Circ Heart Fail*. 2010; 3: 522-27.

[3] Malik FI, Hartman JJ, Elias KA, Morgan BP, Rodriguez H, Brejc K, Anderson RL, Sueoka SH, Lee KH, Finer JT, Sakowicz R. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science*. 2011 Mar 18;331(6023):1439-43.

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