



## **Cytokinetics Announces Non-Clinical Data From Multiple Programs Presented at the Biophysical Society 54th Annual Meeting**

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### **<b>Results Arising From Skeletal and Smooth Muscle Contractility Research Underscore Company's Leadership Position in Programs Directed to Muscle Function</b>**

SOUTH SAN FRANCISCO, CA, Feb 23, 2010 (MARKETWIRE via COMTEX) -- Cytokinetics, Incorporated (NASDAQ: CYTK) announced today that four abstracts regarding its Research & Development programs were presented as posters at the Biophysical Society 54th Annual Meeting, held February 20-24, 2010 at the Moscone Center in San Francisco, California. The posters summarized non-clinical findings arising from Cytokinetics' skeletal and smooth muscle contractility programs, and non-clinical research in oncology. In addition, an oral presentation relating to non-clinical research in oncology was presented.

Poster Presentations at Biophysical Society 54th Annual Meeting

#### **Skeletal Muscle Contractility Program:**

The poster titled "The Small Molecule Skeletal Sarcomere Activator, CK-2017357, is a Calcium Sensitizer that Binds Selectively to the Fast Skeletal Troponin Complex" was presented on Sunday, February 21, 2010 by Raja Kawas, Cytokinetics, Inc., South San Francisco, CA. The objective of the study was to evaluate the selectivity and mechanism of CK-2017357. The authors concluded that CK-2017357 selectively sensitizes the ATPase activity of skinned fast skeletal myofibrils to calcium, without significant activation of myofibrils from slow skeletal or cardiac tissue. Selectivity was demonstrated as activation required the presence of the fast skeletal isoform of troponin; reconstituted sarcomere assays containing slow skeletal or cardiac troponin were not activated by CK-2017357. In addition, isothermal titration calorimetry demonstrated that CK-2017357 binds to purified fast skeletal troponin. Calcium dissociation from fast skeletal troponin was slowed by CK-2017357, consistent with its activating effect on myofibrils at intermediate (but not high and low) calcium concentrations. This compound has also been shown to activate intact fast skeletal muscle sub-maximal force in vitro and in situ, encouraging further studies of the potential therapeutic uses of skeletal muscle troponin activators in diseases where skeletal muscle weakness plays a role.

The poster titled "The Fast Skeletal Troponin Activator, CK-1909178 Reduces Muscle Fatigue in a Model of Peripheral Artery Disease in situ" was presented on Tuesday, February 23, 2010 by Aaron Hinken, Ph.D., Cytokinetics, Inc., South San Francisco, CA. The objective of this study was to evaluate the effects of CK-1909178 on fatigue in native skeletal muscle preparations in vitro, using intact skeletal muscle under normal and hypoxic conditions, and in situ, where nervous input was left intact but the blood supply was limited by occlusion of the femoral artery. The authors concluded that CK-1909178 increased the calcium-sensitivity of force production in skinned fast skeletal muscles. Also, CK-1909178 increased sub-maximal force development in isolated muscle in vitro, and reduced overall fatigue in repeatedly stimulated fast skeletal muscle in normal and hypoxic conditions. CK-1909178 increased sub-maximal force developed in the EDL muscle of rats after arterial administration of compound. In addition, CK-1909178 ameliorated fatigue induced by vascular insufficiency in situ in a rodent model of claudication, when stimulation frequency was adjusted to match tension generation. These data are consistent with the mechanism of action of CK-1909178 as a fast skeletal troponin activator. In skinned muscle fibers, CK-1909178 increased the sensitivity of skeletal muscle to calcium and in living muscle to the frequency of stimulation, each of which resulted in an increase in muscle force development at sub-maximal muscle activation. In addition, CK-1909178 reduced isometric muscle fatigue in vitro in normal and low oxygenated conditions. Moreover, CK-1909178 reduced muscle fatigue in situ when blood supply was restricted. These findings suggest that CK-1909178 and similar other fast skeletal troponin activators may result in functional improvements in skeletal muscle performance and efficiency in conditions marked by muscle weakness by improving the extent of muscle fiber recruitment during physical activity. Finally, these findings indicate that CK-1909178 and similar other fast skeletal troponin activators may have the potential to ameliorate dysfunction induced by peripheral vascular insufficiency, such as exists in intermittent claudication.

#### **Smooth Muscle Contractility Program:**

The poster titled "The Small Molecule Smooth Muscle Myosin Inhibitor, CK-2018571, Selectively Inhibits ATP Hydrolysis and Relaxes Smooth Muscle in vitro" was presented on Monday, February 22, 2010 by Sheila Clancy, Cytokinetics, Inc., South San Francisco, CA. The objective of this study was to determine the selectivity and mechanism of CK-2018571. The authors concluded that CK-2018571 selectively inhibits the ATPase activity of smooth muscle myosin as compared to other myosin II isoforms (e.g., non-muscle myosin, cardiac muscle myosin and skeletal muscle myosin), promoting a weak actin-binding state consistent with its ability to relax smooth muscle tissue in vitro. The authors found that CK-2018571 inhibits the chemical cleavage of ATP by smooth muscle myosin, a mechanism distinct from previously identified myosin inhibitors such as blebbistatin and BTS (N-benzyl-p-toluene sulphonamide). CK-2018571 was shown to inhibit calcium-induced force development in skinned caudal artery and to relax skinned rings activated by thiophosphorylation, consistent with relaxation occurring as a consequence of the direct inhibition of smooth muscle myosin.

#### **Oncology-Related Research:**

The poster titled, "The Molecular Mechanism of the Multi Tasking Kinesin-8 Motor" was presented on Sunday, February 21, 2010 by Carolyn Moores, Ph.D., Birkbeck College, London, United Kingdom. The objective of this study was to determine if kinesin-8 motors have the ability to multi-task by both walking towards microtubule plus-ends and by depolymerizing these ends on arrival, which results in length-dependent depolymerization. Using a combination of crystallography and cryo-EM, the authors concluded that kinesin-8 motors respond to both MT and tubulin substrates, reflecting their multi-tasking activities.

A presentation made during the Motility Subgroup Evening Talk on Saturday, February 20, 2010 by Steven S. Rosenfeld, M.D., Ph.D., Columbia University, New York, NY, included material covering research relating to kinesin spindle protein (KSP), including analyses that demonstrate that Cytokinetics' drug candidate ispinisib, an inhibitor of KSP, blocks transwell migration and reduces glioma cell motility.

## Development Status of CK-2017357

Cytokinetics recently announced data from two Phase I clinical trials evaluating CK-2017357. The first trial is a two part, single-dose, Phase I clinical trial of CK-2017357. Part A of this trial was designed to assess the safety, tolerability and pharmacokinetic profile of increasing single doses of this drug candidate in healthy volunteers and to determine its maximum-tolerated dose and plasma concentration. To date, single doses up to 2000 mg have been administered without causing intolerable adverse events. Part B of this trial was designed to assess the pharmacodynamic effects of CK-2017357 on skeletal muscle function after single oral doses of 250, 500, and 1000 mg, and to assess the relationship of the effects observed to the associated plasma concentrations of CK-2017357. In Part B, CK-2017357 produced concentration-dependent, statistically significant increases versus placebo in the force developed by the tibialis anterior, the muscle evaluated in Part B of this trial, and the doses administered were well-tolerated by the participating healthy volunteers and there were no serious adverse events.

The second trial was a multiple-dose, Phase I clinical trial of CK-2017357 designed to investigate the safety, tolerability and pharmacokinetic profile of CK-2017357 after multiple oral doses to steady state in healthy male volunteers. The trial evaluated doses that produced plasma concentrations in the range associated with pharmacodynamic activity in Part B of the single-dose Phase I study. At steady state, both the maximum plasma concentration and the area under the CK-2017357 plasma concentration versus time curve from before dosing until 24 hours after dosing were generally dose-proportional. In general, systemic exposure to CK-2017357 in this trial was high and inter-subject variability was low. In addition, these multiple-dose regimens of CK-2017357 were well-tolerated, and there were no serious adverse events. The company believes that these results, in combination with the single-dose Phase I clinical trial data, support movement into planned Phase II Evidence of Effect clinical trials in patients with neuromuscular diseases and other conditions that may limit mobility, specifically amyotrophic lateral sclerosis (ALS) and claudication.

### Background on Cytokinetics Skeletal Muscle Contractility Program

CK-2017357 is a fast skeletal muscle troponin activator and is the lead drug candidate from the company's skeletal sarcomere activator program. CK-2017357 selectively activates the fast skeletal troponin complex by increasing its sensitivity to calcium, leading to an increase in skeletal muscle force. This mechanism of action has demonstrated encouraging pharmacological activity in preclinical models that may relate to the potential treatment of diseases associated with aging, muscle wasting or neuromuscular dysfunction. Skeletal muscle contractility is driven by the sarcomere, the fundamental unit of skeletal muscle contraction. It is a highly ordered cytoskeletal structure composed of skeletal muscle myosin, the cytoskeletal motor that is directly responsible for converting chemical energy into mechanical force, actin, and a set of regulatory proteins, troponins and tropomyosin, which make the actin-myosin interaction dependent on changes in intracellular calcium levels. Cytokinetics' skeletal muscle contractility program is focused to the discovery and development of small molecule skeletal sarcomere activators and leverages Cytokinetics' expertise developed in its ongoing discovery and development of cardiac sarcomere activators, including the cardiac myosin activator, omecamtiv mecarbil, now in clinical development as a potential treatment for heart failure. Skeletal sarcomere activators have demonstrated pharmacological activity that may lead to new therapeutic options for diseases associated with aging, muscle wasting, and neuromuscular dysfunction. The clinical effects of muscle wasting, fatigue and loss of mobility can range from decreased quality of life to, in some instances, life-threatening complications. By directly improving skeletal muscle function, a small molecule activator of the skeletal sarcomere may potentially enhance physical performance and quality of life in aging patients.

### Background on Cytokinetics Smooth Muscle Contractility Program

Cytokinetics' smooth muscle research program is directed to smooth muscle myosin, the motor protein responsible for the contraction of the smooth muscle cells that surround airways in the lungs and the blood vessels that control blood pressure. By inhibiting the function of the myosin motor central to the contraction of smooth muscle, these potent small molecules directly lead to the relaxation of contracted smooth muscle. Cytokinetics' smooth myosin inhibitors have demonstrated encouraging pharmacological activity in preclinical models that may relate to uses for the potential treatment of diseases such as systemic hypertension, asthma and chronic obstructive pulmonary disease (COPD). Cytokinetics continues to conduct non-clinical development of its smooth muscle myosin inhibitors.

### About Cytokinetics

Cytokinetics is a clinical-stage biopharmaceutical company focused on the discovery and development of small molecule therapeutics that modulate muscle function for the potential treatment of serious diseases and medical conditions. Cytokinetics' lead drug candidate from its cardiac muscle contractility program, omecamtiv mecarbil (formerly CK-1827452), is in clinical development for the potential treatment of heart failure. Amgen Inc. holds an exclusive license worldwide (excluding Japan) to develop and commercialize omecamtiv mecarbil and related compounds, subject to Cytokinetics' specified development and commercialization participation rights. Cytokinetics is independently developing CK-2017357, a skeletal muscle activator, as a potential treatment for diseases and conditions associated with aging, muscle wasting or neuromuscular dysfunction. Cytokinetics is also conducting non-clinical development of compounds that inhibit smooth muscle contractility and which may be useful as potential treatments for diseases and conditions such as systemic hypertension, pulmonary arterial hypertension or bronchoconstriction. In addition, prior Cytokinetics' research generated three anti-cancer drug candidates that have progressed into clinical development: ispinesib, SB-743921 and GSK-923295. All of these drug candidates and potential drug candidates have arisen from Cytokinetics' research activities and are directed towards the cytoskeleton. The cytoskeleton is a complex biological infrastructure that plays a fundamental role within every human cell. Additional information about Cytokinetics can be obtained at [www.cytokinetics.com](http://www.cytokinetics.com).

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 conduct, design and results of non-clinical studies and clinical trials and the significance and utility of the results of such studies and clinical trials, and the properties and potential benefits of Cytokinetics' drug candidates and potential drug candidates, such as CK-2017357 and Cytokinetics' other skeletal sarcomere activators. 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, 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; Amgen's decisions with respect to the design, initiation, conduct, timing and continuation of development activities for omecamtiv mecarbil; Cytokinetics may incur unanticipated research and development and other costs or be unable to obtain additional financing necessary to conduct development of its products; Cytokinetics may be unable to enter into future collaboration agreements for its drug candidates and programs on acceptable terms, if at all; 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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