



## **Cytokinetics Announces Initiation of Phase I Clinical Trial for Oral Administration of CK-1827452**

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South San Francisco, CA, August 23, 2006 - Cytokinetics, Incorporated (Nasdaq: CYTK) announced the initiation of a Phase I clinical trial evaluating the pharmacokinetic profile of CK-1827452 when administered orally to healthy volunteers. CK-1827452 is a direct cardiac myosin activator under evaluation as a potential treatment for patients with acute and chronic heart failure. A recently-completed Phase I clinical trial in healthy volunteers evaluated an intravenous formulation of CK-1827452. Pharmacokinetic data from that clinical trial suggests that the half-life of CK-1827452 is sufficiently long to support development of an oral dosing.

"We are pleased to initiate this clinical trial to evaluate CK-1827452 administered orally," stated Andrew A. Wolff, M.D., F.A.C.C., Cytokinetics' Senior Vice President of Clinical Research and Development and Chief Medical Officer. "The data from this trial will inform oral formulation development. Our plan is to finalize an oral formulation in order to evaluate a treatment paradigm unavailable with current inotropic agents which can only be administered intravenously. We look forward to the possibility of initiating intravenous treatment of CK-1827452 in acutely decompensated heart failure patients in a hospital setting, transitioning to chronic oral therapy before discharge. Furthermore, we believe patients with chronic heart failure may also benefit from initiation of oral CK-1827452 in an outpatient setting. Development of an oral formulation of CK-1827452 is therefore important to the Phase II and Phase III studies we are planning to conduct in order to critically evaluate this potential intravenous-to-oral treatment paradigm."

Data from the Phase I clinical trial of CK-1827452 administered intravenously is planned to be presented at a session entitled "Recent and Late Breaking Trials" at the 10th Annual Meeting of the Heart Failure Society of America on Wednesday, September 13, 2006 in Seattle, Washington. The presentation will be made by John R. Teerlink, M.D., F.A.C.C., F.A.H.A., F.E.S.C., Associate Professor of Medicine at the University of California, San Francisco, and Director of the Heart Failure Clinic, Veterans Affairs Medical Center, San Francisco. Dr. Teerlink is a Co-Principal Investigator and responsible for echocardiographic analysis for this Phase I clinical trial.

### **Development Status of CK-1827452**

A Phase I, first-in-humans clinical trial designed to evaluate CK-1827452, a novel, small-molecule, direct activator of cardiac myosin, has recently been completed with an intravenous formulation in healthy volunteers. The clinical activity of CK-1827452 in that clinical trial is consistent with results from preclinical models which evaluated this drug candidate in both normal dogs and dogs with heart failure. In these preclinical models, underlying the increase in ejection fraction and fractional shortening was a dose-related increase in the systolic ejection time, which has now also been observed in humans. Data presented at the 2005 Annual Meeting of the Heart Failure Society of America from a dog model of heart failure demonstrated that CK-1827452, administered as a 0.5 mg/kg bolus followed by a 3-4 hour infusion at 0.5 mg/kg/hr, increased cardiac contractility and cardiac output without increasing myocardial oxygen consumption. Preclinical studies have also demonstrated more pronounced effects of CK-1827452 on indices of cardiac function in dogs with heart failure compared to effects achieved in normal dogs.

Cytokinetics expects that CK-1827452 will be entering an international Phase II clinical trials program in patients with heart failure in the second half of 2006. This program is planned to evaluate CK-1827452 in a diversity of patients including those with stable heart failure, inducible ischemia, impaired renal function and acute heart failure. This program is designed to test the safety and efficacy of CK-1827452, in both intravenous and oral formulations, for the potential treatment of heart failure across the continuum of care, both in the hospitalized setting and in the outpatient setting.

### **Background on the Heart Failure Market**

Heart failure is a widespread and debilitating syndrome affecting approximately five million people in the United States alone. The high and rapidly growing prevalence of heart failure translates into significant hospitalization rates and associated societal costs. The number of hospital discharges in the United States identified with a primary diagnosis of heart failure rose from 550,000 in 1989 to over 1 million in 2003. Heart failure is one of the most common primary discharge diagnoses identified in hospitalized patients over the age of 65 in the United States. The annual costs of heart failure in the United States are estimated to be \$29.6 billion, including \$19.3 billion for inpatient care. According to industry reports, the U.S. market for heart failure drugs was approximately \$1.33 billion in 2004. Despite currently available therapies, readmission rates for patients over the age of 65 remain high at 30 to 40 percent within six months of hospital discharge and mortality rates exceed 50% over a five year period following a diagnosis of acute heart failure. The limited effectiveness of current therapies points to the need for next-generation therapeutics that may offer improved efficacy without increased adverse events.

### **Background on Cardiac Myosin Activators and Cardiac Contractility**

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 contractility is driven by the cardiac sarcomere, a highly ordered cytoskeletal structure composed of cardiac myosin, actin and a set of regulatory proteins, and is the fundamental unit of muscle contraction in the heart. The sarcomere represents one of the most thoroughly characterized protein machines in human biology. Cytokinetics' cardiovascular program is focused towards the discovery and development of small molecule cardiac myosin activators in order to create next-generation treatments to manage acute and chronic heart failure. Cytokinetics' program is based on the hypothesis that activators of cardiac myosin may address certain mechanistic liabilities of existing positive inotropic agents by increasing cardiac contractility without increasing intracellular calcium, which may be associated with adverse clinical effects in heart failure patients. Current inotropic agents, such as beta-adrenergic receptor agonists or inhibitors of phosphodiesterase activity, increase cardiac cell contractility by increasing the concentration of intracellular calcium, which indirectly activates cardiac myosin; this effect on calcium levels, however, also has been linked to potentially life-threatening side effects. The inotropic mechanism of current drugs also increases the velocity of cardiac contractility and shortens systolic ejection time. In contrast, cardiac myosin activators have been shown to work in the absence of changes in intracellular calcium by a novel mechanism that directly stimulates the activity of the cardiac myosin motor protein. Cardiac myosin activators accelerate the rate-limiting step of the myosin enzymatic cycle and shift the enzymatic cycle in favor of the force producing state. This calcium-independent inotropic mechanism results not in an increase in the velocity of cardiac contraction, but instead, a lengthening of the systolic ejection time, which results in increased cardiac contractility and cardiac output in a potentially more oxygen-efficient manner.

### **About Cytokinetics**

Cytokinetics is a biopharmaceutical company focused on the discovery, development and commercialization of novel small molecule drugs that

specifically target the cytoskeleton. The cytoskeleton is a complex biological infrastructure that plays a fundamental role within every human cell. Cytokinetics' focus on the cytoskeleton enables it to develop novel and potentially safer and more effective classes of drugs directed at treatments for cancer, cardiovascular disease and other diseases. Under a strategic alliance established in 2001, Cytokinetics and GlaxoSmithKline (GSK) are collaborating to develop and commercialize small molecule therapeutics targeting human mitotic kinesins for applications in the treatment of cancer and other diseases. Ispinesib (SB-715992), SB-743921 and GSK-923295 are being developed under the strategic alliance with GSK. GSK is conducting Phase II and Ib clinical trials for ispinesib and a Phase I clinical trial for SB-743921, and Cytokinetics is conducting a Phase I/II trial of SB-743921 in non-Hodgkin's lymphoma. Cytokinetics' unpartnered cardiovascular disease program is the second program to leverage the company's expertise in cytoskeletal pharmacology. Cytokinetics recently completed a Phase I clinical trial with CK-1827452, a novel small molecule cardiac myosin activator, for the intravenous treatment of heart failure and also is advancing CK-1827452 as a potential drug candidate for the treatment of chronic heart failure via oral administration. Additional information about Cytokinetics can be obtained at <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 Safe Harbor for forward-looking statements contained in the Act. Examples of such statements include, but are not limited to, statements about the timing, scope and focus of Cytokinetics' clinical research and development activities with respect to CK-1827452, the size and growth of expected markets for CK-1827452, the potential benefits of CK-1827452, the possibility of new treatment paradigms using CK-1827452, the potential benefits of Cytokinetics' other drug candidates and potential drug candidates, and the benefits of data obtained from completed clinical trials. Such statements are based on management's current expectations, but actual results may differ materially due to various factors. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to difficulties or delays in patient enrollment for clinical trials, unexpected adverse side effects or inadequate therapeutic efficacy of CK-1827452 or Cytokinetics' other drug candidates and other potential difficulties or delays in development, testing, regulatory approval, production and marketing of CK-1827452 or Cytokinetics' other drug candidates that could slow or prevent clinical development, product approval or market acceptance (including the risks relating to uncertainty of patent protection for Cytokinetics' intellectual property or trade secrets, Cytokinetics' ability to obtain additional financing if necessary and unanticipated research and development and other costs), changing standards of care and the introduction of products by competitors or alternative therapies for the treatment of indications currently or potentially targeted by CK-1827452 and the implementation and maintenance of procedures, policies, resources and infrastructure relating to compliance with new or changing laws, regulations and practices. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission.