



## **Cytokinetics Announces Clinical Trials Data Relating to CK-1827452 Presented at the 2008 Annual Heart Failure Society of America Conference**

September 24, 2008 1:16 PM EDT

### **Interim Analysis of Ongoing Phase IIa Clinical Trial Demonstrates Statistically Significant Correlations Between Measures of Cardiac Systolic Performance and CK-1827452 Plasma Concentrations**

SOUTH SAN FRANCISCO, CA, Sep 24, 2008 (MARKET WIRE via COMTEX News Network) -- Cytokinetics, Incorporated (NASDAQ: CYTK) announced today that a Late Breaking oral presentation and a poster presentation, each relating to one of two clinical trials for CK-1827452, were presented at the 2008 Annual Heart Failure Society of America (HFSA) Conference, which is being held September 21-24, 2008 at the Metro Toronto Convention Centre in Toronto, Ontario, Canada. These trials, conducted in stable heart failure patients, are evaluating CK-1827452, a novel cardiac myosin activator being developed for the potential treatment of patients with either acutely decompensated or chronic heart failure.

#### **Oral Presentation at HFSA**

An oral presentation entitled, "The Selective Cardiac Myosin Activator CK-1827452 Increases Systolic Function in a Concentration-Dependent Manner in Patients with Stable Heart Failure," was presented in the Late Breaking Clinical Trials: II, Symposium XXVII on Wednesday, September 24, 2008, by John Cleland, MD, FACC, FRCP, FESC, Professor of Cardiology, Castle Hill Hospital, University of Hull, United Kingdom. The presentation included data from eight patients from each of Cohorts 1, 2 and 3 and four patients from Cohort 4. These interim analyses demonstrated statistically significant correlations between CK-1827452 plasma concentration and increases in systolic ejection time, stroke volume, fractional shortening (each  $p < 0.0001$ ), cardiac output ( $p < 0.01$ ), and ejection fraction ( $p < 0.05$ ). These correlations between CK-1827452 plasma concentration and increases in parameters of cardiac systolic function remained evident after 24 hours of intravenous infusion. In addition, there were statistically significant correlations between CK-1827452 concentration and decreases in heart rate ( $p < 0.001$ ) and left ventricular end-systolic volume ( $p < 0.05$ ). Decreases in left ventricular end-diastolic volume were not statistically significant. CK-1827452 was well-tolerated in stable heart failure patients over a range of plasma concentrations during continuous intravenous administration. Although concentration-related increases in ejection time were observed, the proportion of the cardiac cycle dedicated to ejection remained relatively constant, due to the decline in heart rate at higher concentrations.

"These additional data add to the growing body of evidence supporting the potentially clinically useful pharmacodynamic effects of intravenous CK-1827452 in stable heart failure patients. The unique mechanism of action of CK-1827452 increases stroke volume without an increase in energy expenditure and holds great promise for the treatment of heart failure," stated Dr. Cleland. "This clinical trial is progressing well into its final phases and has contributed hypothesis-generating data which merits further study in additional outcomes-oriented clinical trials in the future in larger heart failure patient populations."

"The observation that increasing plasma concentrations of CK-1827452 continue to be associated with increasing effects on systolic function, even after 24 hours of intravenous infusion, adds further support to our therapeutic hypothesis that prolonged treatment with CK-1827452 may continue to be associated with these potentially useful increases in parameters of cardiac pump function in patients with heart failure due to systolic dysfunction," stated Andrew A. Wolff, MD, FACC, Cytokinetics' Senior Vice President of Clinical Research and Development and Chief Medical Officer. "With these additional data, a statistically significant correlation between increases in ejection fraction and plasma concentrations of CK-1827452 has been demonstrated for the first time."

#### **Poster Presentation at HFSA**

A poster entitled, "Rationale and Design for a Phase II Study Evaluating the Effect of the Cardiac Myosin Activator, CK-1827452, on Cardiac Function, Hemodynamics, and Myocardial Oxygen Consumption in Patients with Heart Failure," was presented on Tuesday, September 23, 2008 by John Parker, MD, FRCP (C), Professor of Medicine and Pharmacology, University of Toronto, Mount Sinai and University Networks Hospital. This poster presentation outlined the design of a Phase IIa clinical trial intended to evaluate CK-1827452 in patients with heart failure undergoing cardiac catheterization. This Phase IIa clinical trial is designed to test the hypothesis that CK-1827452 can improve cardiac function and hemodynamics without significantly altering myocardial oxygen consumption and thus improve cardiac efficiency. The primary objective of this trial is to evaluate the potential effects of CK-1827452 on myocardial efficiency, defined as the ratio of ventricular performance to myocardial oxygen consumption. The secondary objectives of this trial are to measure the potential effects of CK-1827452 on ventricular performance, myocardial oxygen consumption, hemodynamics, pressure-volume relationships and systolic ejection time. Preclinical studies have suggested that CK-1827452 increases ventricular performance in the absence of substantial changes in myocardial oxygen consumption, thereby increasing myocardial efficiency. This trial of CK-1827452 is designed to investigate this finding further in patients with stable heart failure. The protocol for this clinical trial provides for the enrollment of two cohorts of patients. The first cohort, consisting of six patients, will undergo a dose escalation phase, beginning with a target plasma concentration of approximately 280 ng/mL. Based on the tolerability and pharmacodynamic effects observed in this initial cohort, the investigators will select a single dosing regimen to administer to the second cohort, consisting of twelve patients. This clinical trial is enrolling patients and has initiated dosing.

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

CK-1827452 is currently the subject of a clinical trials program comprised of multiple Phase I and Phase IIa trials. This program is designed to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetic profile of both intravenous and oral formulations of CK-1827452 for the potential treatment of heart failure across the continuum of care, in both hospital and outpatient settings.

Earlier in 2008, in Munich, Germany at the European Society of Cardiology Congress 2008 and in Milan, Italy at the Heart Failure Congress, Cytokinetics announced results from interim analyses for the above mentioned Phase IIa clinical trial of CK-1827452 in patients with stable heart failure. In these interim analyses, the authors concluded that CK-1827452 increases measures of cardiac systolic performance in a concentration-dependent manner. Based on these interim results, CK-1827452 appeared to be well-tolerated in stable heart failure patients over a broad range of plasma concentrations during continuous intravenous administration.

In April 2008, Cytokinetics initiated a Phase IIa trial that is designed to evaluate an intravenous formulation together with an oral formulation of CK-1827452 in patients with ischemic cardiomyopathy and angina. The primary objective of this double-blind, randomized, placebo-controlled Phase IIa clinical trial is to assess the effect of intravenous CK-1827452 on symptom-limited treadmill exercise tolerance. The secondary objective of this trial is to assess the tolerability and resulting plasma concentrations of CK-1827452 administered as an oral formulation. The trial is designed to evaluate two cohorts of 45 patients each with ischemic cardiomyopathy and angina and an ejection fraction of less than or equal to 35 percent. Based on the Safety Review Committee's recommendation following its review of safety data from Cohort 1 of this trial, in August 2008, Cytokinetics opened enrollment in Cohort 2, which recently commenced patient dosing.

Cytokinetics has conducted five Phase I clinical trials of CK-1827452 in healthy subjects: a first-time-in-humans study evaluating an intravenous formulation, an oral bioavailability study evaluating both intravenous and oral formulations, and three studies of oral formulations: a drug-drug interaction study, a dose proportionality study and a study evaluating modified-release formulations. Data from each of these trials have been reported previously.

#### 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. 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 further activates the cardiac sarcomere. 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 contraction 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 inotropic mechanism results not in an increase in the velocity of cardiac contraction, but instead, in 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 may address areas of significant unmet clinical needs. Cytokinetics' cardiovascular disease program is focused to cardiac myosin, a motor protein essential to cardiac muscle contraction. Cytokinetics' lead compound from this program, CK-1827452, a novel small molecule cardiac myosin activator, entered Phase II clinical trials for the treatment of heart failure in 2007. Under a strategic alliance established in 2006, Cytokinetics and Amgen Inc. are performing joint research focused on identifying and characterizing activators of cardiac myosin as back-up and follow-on potential drug candidates to CK-1827452. Amgen has obtained an option for an exclusive license to develop and commercialize CK-1827452, subject to Cytokinetics' development and commercial participation rights. Cytokinetics' cancer program is focused on mitotic kinesins, a family of motor proteins essential to cell division. Under a strategic alliance established in 2001, Cytokinetics and GlaxoSmithKline (GSK) are conducting research and development activities focused on the potential treatment of cancer. Cytokinetics is developing two novel drug candidates that have arisen from this program, ispinesib and SB-743921, each a novel inhibitor of kinesin spindle protein (KSP), a mitotic kinesin. Cytokinetics is conducting a Phase I clinical trial of ispinesib as monotherapy as a first-line treatment in chemotherapy-naïve patients with locally advanced or metastatic breast cancer. In addition, Cytokinetics is conducting a Phase I trial of SB-743921 in patients with non-Hodgkin or Hodgkin lymphoma. GSK has an option for the joint development and commercialization of ispinesib and SB-743921. Cytokinetics and GSK are conducting collaborative research activities directed to the mitotic kinesin centromere-associated protein E (CENP-E). GSK-923295, a CENP-E inhibitor, is being developed under the strategic alliance by GSK; GSK began a Phase I clinical trial with GSK-923295 in 2007. In April 2008, Cytokinetics announced the selection of a potential drug candidate directed towards skeletal muscle contractility which may be developed as a potential treatment for skeletal muscle weakness associated with neuromuscular diseases or other conditions. 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' research and development programs, including the design, enrollment, conduct and results of its clinical trials for CK-1827452 and the properties and potential clinical benefits of CK-1827452 and Cytokinetics' other drug candidates and potential 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 approval or production of CK-1827452 or Cytokinetics' other 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, including, but not limited to, difficulties or delays due to political instability in countries where clinical trials of CK-1827452 or Cytokinetics' other drug candidates are being conducted, CK-1827452 or Cytokinetics' other 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 and others may introduce products or alternative therapies for the treatment of indications CK-1827452 or Cytokinetics' other drug candidates and potential drug candidates may target; and risks and uncertainties relating to Amgen's and GSK's decisions as to whether to exercise their respective options and the timing and receipt of payments, including option fees, milestones and royalties on future potential product sales under Cytokinetics' respective agreements with Amgen and GSK. 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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