Cytokinetics Announces Initiation of Phase II Clinical Trials Program for CK-1827452

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First Patient Dosed in a Phase IIa Clinical Trial Evaluating CK-1827452 in Patients with Stable Heart Failure

SOUTH SAN FRANCISCO, Calif., April 12 /PRNewswire-FirstCall/ -- Cytokinetics, Incorporated (Nasdaq: CYTK) announced today the initiation of a Phase II clinical trials program evaluating CK-1827452, a novel cardiac myosin activator for the potential treatment of patients with either acutely decompensated or chronic heart failure. The first patient has been dosed in the first Phase IIa clinical trial, which is designed to evaluate the safety, tolerability, pharmacodynamic and pharmacokinetic profile of an intravenous formulation of CK-1827452 in patients with stable heart failure. CK-1827452 is the subject of a Collaboration and Option Agreement recently executed by Cytokinetics with Amgen Inc.

This first Phase II clinical trial, now underway in the United Kingdom, is a multi-center, double-blind, randomized, placebo-controlled, dose-escalation, pharmacokinetic and pharmacodynamic study of CK-1827452 in patients with stable heart failure. The primary objective of this trial is to evaluate the safety and tolerability of CK-1827452 administered as an intravenous infusion to stable heart failure patients. The secondary objectives of this trial are to establish a relationship between plasma concentration and pharmacodynamic effect for CK-1827452 and to determine the pharmacokinetics of CK-1827452 in stable heart failure patients. In addition to routine assessments of vital signs, blood samples and ECG monitoring, echocardiograms will be performed to evaluate cardiac function at various pre-defined time points.

The clinical trial will consist of at least five cohorts of eight patients with stable heart failure. The first three of these cohorts will each undergo four treatment periods; patients will receive three escalating active doses of CK-1827452 administered intravenously and one placebo treatment which will be randomized into the dose escalation sequence. Patients in the fourth and fifth cohorts are planned to receive only a single dose level of CK-1827452. In each cohort, patients will receive a one-hour loading infusion to rapidly achieve a target plasma concentration of CK-1827452, followed by a slower infusion intended to maintain that plasma concentration. These maintenance infusions are planned to be one hour in duration in the first two cohorts, and 23 hours in duration in the last three cohorts.

This first Phase II clinical trial for CK-1827452 is part of a clinical trials program, to be conducted by Cytokinetics, which is planned to be comprised of Phase I and Phase II trials designed to evaluate the safety and efficacy of CK-1827452 in a diversity of patients, including those with stable heart failure, ischemic heart disease, impaired renal function and acutely decompensated heart failure, and patients with chronic heart failure at increased risk for death and hospital admission for heart failure. These trials are planned to evaluate 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, in both hospital and outpatient settings.

"We are pleased to initiate the Phase II clinical trials program for CK- 1827452," 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 first Phase IIa clinical trial will help us to select dosing regimens for further study in later clinical trials of CK-1827452 in patient populations with heart failure of increasing severity."

Additional Phase I Clinical Trial

Cytokinetics also recently initiated an additional Phase I clinical trial with CK-1827452 in the United Kingdom. This clinical trial is a single-center, open-label, sequential, parallel group study designed to evaluate the potential for certain drug-drug interactions with CK-1827452. The trial is designed to evaluate the effects of ketoconazole, a strong CYP3A4 inhibitor, on the pharmacokinetics of CK-1827452 in sixteen healthy male volunteers. If a significant pharmacokinetic interaction between CK-1827452 and ketoconazole is identified, then a second stage of the clinical trial will be initiated. This second stage is designed to evaluate the effects of diltiazem, a moderate CYP3A4 inhibitor, on the pharmacokinetics of CK-1827452 in an additional cohort of eight healthy male volunteers.

Development Status of CK-1827452

Data from the first-in-humans Phase I clinical trial of CK-1827452 administered intravenously were previously announced at the Heart Failure Society of America annual meeting in Seattle in September 2006 and the American Heart Association Scientific Sessions in November 2006. This clinical trial demonstrated that the maximum tolerated dose (MTD) was 0.5 mg/kg/hr for the six-hour infusion in healthy volunteers. At this dose, the six-hour infusion of CK-1827452 produced a statistically significant increase in left ventricular ejection fraction as compared to placebo ($p<0.0001$). At the same dose, CK-1827452 also produced a statistically significant increase in fractional shortening versus placebo ($p<0.0001$). These increases in indices of left ventricular function were associated with a mean prolongation of systolic ejection time ($p<0.0001$). These mean changes in ejection fraction, fractional shortening and systolic ejection time were dose-proportional across the range of doses evaluated in this clinical trial. In addition, CK-1827452 exhibited linear, dose-proportional pharmacokinetics across the range of doses studied. At the MTD of 0.5 mg/kg/hr for 6 hours and below, CK-1827452 was well-tolerated when compared to placebo.

The adverse effects at intolerable doses in humans appeared similar to the adverse findings observed in the preclinical safety studies which occurred at similar plasma concentrations. These effects are believed to be related to an excess of the intended pharmacologic effect, resulting in excessive prolongation of the systolic ejection time, and resolved promptly with discontinuation of the infusions of CK-1827452. Pharmacokinetic data from this completed Phase I clinical trial suggested that the half-life of CK- 1827452 was sufficient to support development of an oral dosing formulation.

In December 2006, Cytokinetics announced the results of a Phase I oral bioavailability study. Pharmacokinetic data from this study demonstrated oral bioavailability of approximately 100% for each of the three conditions of oral administration. These data suggest relatively little variability in oral absorption between subjects and therefore predictable plasma levels with oral administration of CK-1827452, which may help to ensure the safety and tolerability of CK-1827452 during chronic oral administration. Analysis of the combined pharmacokinetic data from this oral bioavailability study and from the first-in-humans study (in which healthy volunteers received intravenous CK-1827452) supports dosing CK-1827452 both intravenously and orally without requiring adjustment for patient weight.

Background on Amgen Collaboration

In January 2007, Cytokinetics and Amgen announced a strategic collaboration to discover, develop and commercialize novel small-molecule therapeutics that activate cardiac muscle contractility for potential applications in the treatment of heart failure. In addition, Amgen obtained an option to participate in the future development and commercialization of Cytokinetics' lead drug candidate, CK-1827452, and other drug candidates arising from the

collaboration. The collaboration is worldwide, excluding Japan. Under the agreement, Cytokinetics received approximately $75 million, comprised of a non-refundable up-front license and technology access fee of $42 million and equity investment of approximately $33 million.

Joint research activities will focus on identifying and characterizing activators of cardiac myosin as back-up and follow-on potential drug candidates to CK-1827452. During the initial two-year research term, in addition to performing research at its own expense under the collaboration, Cytokinetics will continue to conduct all development activities for CK- 1827452, at its own expense, subject to Amgen's option and according to an agreed development plan. Amgen's option is exercisable during a defined period, the ending of which is dependent upon the satisfaction of certain conditions, including CK-1827452 being developed to meet pre-defined criteria in Phase IIa clinical trials. To exercise its option, Amgen would pay a non- refundable exercise fee of $50 million and thereafter would be responsible for development and commercialization of CK-1827452 and related compounds, subject to development and commercial participation rights of Cytokinetics. In addition, Cytokinetics may be eligible to receive pre-commercialization and commercialization milestone payments of up to $600 million on CK-1827452 and other products arising from the research, as well as escalating royalties. Cytokinetics also has the opportunity to earn increased royalties by participating in Phase III development costs. In that case, Cytokinetics could co-promote products in North America and would be expected to play a significant role in the agreed commercial activities. If Amgen elects not to exercise its option on CK-1827452, Cytokinetics may then proceed to independently develop CK-1827452 and the research collaboration would terminate.

Background on the Heart Failure Market

Heart failure is a widespread and debilitating syndrome affecting approximately 5 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 2004. 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 $1.3 billion in 2004. Despite currently available therapies, readmission rates for patients over the age of 65 remain high as high as 42% within one year of hospital discharge and mortality rates are approximately 60% over the 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. 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 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 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' development efforts are directed to advancing multiple drug candidates through clinical trials to demonstrate proof-of-concept in humans, specifically in the areas of heart failure and cancer. Cytokinetics' cardiovascular disease program is focused to cardiac myosin, a motor protein essential to cardiac muscle contraction. Cytokinetics' lead compound, CK-1827452, a novel small molecule cardiac myosin activator, entered Phase II clinical trials for the treatment of heart failure in early 2007. Under a strategic alliance established in 2006, Cytokinetics and Amgen will conduct research with activators of cardiac myosin in order to identify potential treatments for patients with heart failure. Amgen has obtained an option for the joint development and commercialization of CK-1827452 exercisable during a defined period, the ending of which is dependent on Cytokinetics' conduct of further clinical trials of CK-1827452. Cytokinetics' cancer program is focused to mitotic kinesins, a family of motor proteins essential to cell division. 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. Ispinesib has been the subject of a broad clinical trials program comprised of nine Phase II clinical trials as well as six Phase I or Ib clinical trials. Cytokinetics plans to conduct additional clinical trials with ispinesib and is conducting a Phase I/II trial of SB-743921 in non-Hodgkin's lymphoma. Under a strategic alliance established in 2001, Cytokinetics and GlaxoSmithKline (GSK) are conducting research and development activities focused towards the potential treatment of cancer. GSK has obtained an option for the joint development and commercialization of ispinesib and SB-743921, exercisable during a defined period. 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 is expected to begin clinical trials with GSK-923295 in 2007. All of these 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. Cytokinetics' focus on the cytoskeleton enables it to develop novel and potentially safer and more effective classes of drugs directed at treatments for cancer, and cardiovascular disease. Additional information about Cytokinetics can be obtained at 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 regarding expected initiation, timing, scope and targeted indications of clinical trials within Cytokinetics' and its partners' clinical development and research programs, including Cytokinetics' clinical research and development activities with respect to CK-1827452, and the potential benefits of data obtained from completed clinical trials; potential milestone payments and other payments and funding under Cytokinetics' collaboration with Amgen and Cytokinetics' and Amgen's expected roles in developing or commercializing drug candidates or drugs subject to that collaboration; the potential benefits of CK-1827452 and other potential drug candidates that may be developed under the collaboration and of Cytokinetics' other drug candidates and potential drug candidates; the size and growth of expected markets for heart failure therapeutics, including CK-1827452; and the enabling capabilities of Cytokinetics' biological focus. 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 decisions by GSK to discontinue its research or development efforts for GSK-923295 under Cytokinetics' collaboration with GSK; difficulties or delays in patient enrollment for clinical trials; unexpected adverse side effects or inadequate therapeutic efficacy of Cytokinetics' drug candidates, including CK-1827452; other potential difficulties or delays in development, testing, regulatory approval, production and marketing of Cytokinetics' drug candidates that could slow or prevent clinical development, product approval or market acceptance (including the risks relating to uncertainty of patent or trade secret protection for Cytokinetics' intellectual property, Cytokinetics' ability to obtain additional financing if necessary and unanticipated research and development and other costs); and changing standards of care and the introduction by others of products or alternative therapies for the treatment of indications currently or potentially targeted by Cytokinetics' drug candidates,

including CK-1827452. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission.

SOURCE Cytokinetics, Incorporated

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