



Cytokinetics Announces Preclinical Data for CK-3773274 Presented at the American Chemical Society Spring 2021 Virtual Meeting

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Next-In-Class Cardiac Myosin Inhibitor Optimized for Shallow Exposure Response and Pharmacokinetics to Enable Flexible Dose Titration

SOUTH SAN FRANCISCO, Calif., April 12, 2021 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that data related to the optimization of CK-3773274 (CK-274), including the first disclosure of its chemical structure, were presented at the American Chemical Society Spring 2021 Virtual Meeting. The presentation reviewed scientific activities that involved evaluating CK-274 and precursor compounds for their exposure-response relationship, projected human half-life, and potential for meaningful cytochrome P450 (CYP450) interactions. CK-274 is a next-in-class cardiac myosin inhibitor discovered by company scientists, in development for the potential treatment of hypertrophic cardiomyopathy (HCM).

"These preclinical data provide a first look at the structure of our next-in-class cardiac myosin inhibitor, CK-274, and its performance in certain preclinical assays," said Brad Morgan, Ph.D., Cytokinetics' Senior Vice President, Research and Non-Clinical Development. "CK-274 was synthesized from a newly discovered and distinct chemical series following an optimization program that was intentionally focused on key compound physiochemical characteristics, such as a shallow dose-response relationship and a half-life that may enable flexible and timely dosing adjustments. We look forward to results from REDWOOD-HCM, the Phase 2 clinical trial of CK-274, which is designed to elaborate on how these differentiated properties may translate into its potential use in patients with obstructive HCM."

Data presented described the primary optimization objectives, identification of an initial hit compound, and its subsequent chemical optimization, including preclinical characterization in biochemical assays, cardiac myocytes, and *in vivo* models of cardiac function. In cardiac myofibrils, the biochemical potency of CK-274 was 1.26 μM and it reduced cardiac myocyte contractility to 33% of baseline at 5 μM . Echocardiographic data from healthy rats showed that CK-274 reduced fractional shortening, a measure of cardiac function, in a dose- and exposure-dependent fashion. The pharmacodynamic window, characterized by the ratio of plasma concentrations required to achieve a 50% (IC_{50}) and 10% (IC_{10}) reduction in fractional shortening ($\text{IC}_{50}/\text{IC}_{10}$) was 9.6 for CK-274. The exposure-response relationship for CK-274 in healthy dogs was similar to that observed in rats.

Preclinical pharmacokinetic characterization of CK-274 suggested its predicted half-life in humans was 2.8 days¹. This projection was borne out in the first-in-human Phase 1 study of CK-274 in healthy volunteers in which the single dose administered half-life was observed to be 3.4 days², and steady-state was reached within 2 weeks following multiple doses. Reaching steady state within two weeks may translate to ease of dose titration and onset of action in patients with obstructive HCM, as well as timely reversibility of effect if discontinuation is necessary. CK-274 was designed to have a low potential to inhibit representative human CYP450s in order to reduce the potential for drug-drug interactions. CK-274 did not exhibit direct or time dependent inhibition of seven human CYP isoforms ($\text{IC}_{50} > 30 \mu\text{M}$ for 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4).

Comparison of CK-274 to *mavacamten*, a cardiac myosin inhibitor, whose precursor was discovered by Cytokinetics' scientists and subsequently optimized in collaboration with Myokardia, Inc. and now being developed by Bristol-Myers Squibb Company, was also performed in certain preclinical assays. The presentation from the American Chemical Society Spring 2021 Virtual Meeting can be found at <https://cytokinetics.com/publications-and-presentations>.

Together, these data suggest that CK-274 may be a next-in-class, cardiac myosin inhibitor with a shallow pharmacokinetic/pharmacodynamic relationship and pharmacokinetics that may provide for flexible dose titration. The efficacy and safety of CK-274 are now being evaluated in patients with obstructive HCM.

About CK-274

CK-274 is a novel, oral, small molecule cardiac myosin inhibitor arising 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 well suited in conditions characterized by excessive hypercontractility, such as HCM.

In preclinical models of cardiac function, CK-274 reduced cardiac contractility in a predictable dose and exposure dependent fashion. In preclinical models of disease, CK-274 reduced compensatory cardiac hypertrophy and cardiac fibrosis. The preclinical pharmacokinetics of CK-274 were characterized, evaluated and optimized for potential ease of titration. Previously presented data from the Phase 1 study of CK-274 demonstrated that it was well tolerated in healthy participants and that the shallow exposure-response relationship observed preclinically appeared to translate to humans.¹

REDWOOD-HCM: Clinical Trial Design

REDWOOD-HCM is a multi-center, randomized, placebo-controlled, double-blind, dose finding clinical trial of CK-274 in patients with symptomatic obstructive HCM (oHCM). The primary objective of the trial is to determine the safety and tolerability of CK-274. The secondary objectives are to describe the concentration-response relationship of CK-274 on the resting and post-Valsalva left ventricular outflow tract gradient as measured by echocardiography during 10 weeks of treatment, to describe the dose response relationship of CK-274, and to evaluate the plasma concentrations of CK-274 in patients with oHCM.

The trial will enroll two sequential cohorts, with an option for a third cohort. Within each cohort, approximately 18 patients will be randomized 2:1 to active or placebo treatment and receive up to three escalating doses of CK-274 or placebo based on echocardiographic guidance. Patients receive an echocardiogram after two weeks of treatment at each dose to determine whether they will be up-titrated. Overall, the treatment duration will be 10 weeks with an echocardiogram to confirm reversibility of effect 2-weeks after the last dose. REDWOOD-HCM is expected to enroll patients in

approximately 20 investigative sites in North America and Europe.

Interim analysis of data from Cohort 1 of REDWOOD-HCM showed patients experienced substantial reductions in the average resting left ventricular outflow tract gradient (LVOT-G) as well as the post-Valsalva LVOT-G (defined as resting gradient <30 mmHg and post-Valsalva gradient <50 mmHg). These clinically relevant decreases in pressure gradients were achieved with only modest decreases in average left ventricular ejection fraction (LVEF); there were no dose interruptions due to LVEF falling below 50%, the prespecified safety threshold. Pharmacokinetic data were similar to those observed in Phase 1 in healthy subjects. In addition, the safety and tolerability data were supportive of continued dose escalation with no serious adverse events attributed to study treatment reported by the investigators.

Enrollment in Cohort 2 of REDWOOD-HCM completed in Q1 2021 and full results from REDWOOD-HCM, across both Cohort 1 and Cohort 2, are expected in mid-2021.

Additional information about REDWOOD-HCM can be found on www.clinicaltrials.gov.

About Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a disease 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. 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 atrial fibrillation, stroke and death due to arrhythmias. There are no FDA approved 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 conducting regulatory interactions for *omecamtiv mecarbil*, its novel cardiac muscle activator, following positive results from GALACTIC-HF, a large, international Phase 3 clinical trial in patients with heart failure. Cytokinetics is conducting METEORIC-HF, a second Phase 3 clinical trial of *omecamtiv mecarbil*. Cytokinetics is also developing CK-274, a next-generation cardiac myosin inhibitor, for the potential treatment of hypertrophic cardiomyopathies (HCM). Cytokinetics is conducting REDWOOD-HCM, a Phase 2 clinical trial of CK-274 in patients with obstructive HCM. Cytokinetics is also developing *reldesemtiv*, a fast skeletal muscle troponin activator for the potential treatment of ALS and other neuromuscular indications following conduct of FORTITUDE-ALS and other Phase 2 clinical trials. The company is preparing for the potential advancement of *reldesemtiv* to a Phase 3 clinical trial in ALS. 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 2 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. P Cremin, et al. Poster # 887215 presented at AAPS annual meeting, Atlanta, Georgia, October 28-November 5, 2020
2. LA Robertson, et al. Poster #210 presented at the 23rd HFSA Annual Scientific Meeting, September 13–16, 2019, Philadelphia, PA, USA



Source: Cytokinetics, Incorporated