Cytokinetics Announces Additional Results from GALACTIC-HF Presented at American Heart Association Scientific Sessions 2021

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Analysis from GALACTIC-HF Shows Treatment with Omecamtiv Mecarbil Associated with Significant Reduction in the Risk of Stroke

Data on Analog to CK-3828136 Adds Preclinical Support for Cardiac Troponin Activation as Novel Mechanism to Increase Cardiac Function without Impacting Cardiac Efficiency

SOUTH SAN FRANCISCO, Calif., Nov. 15, 2021 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that additional results from GALACTIC-HF (**G**lobal **A**pproach to **L**owering **A**dverse **C**ardiac Outcomes **T**hrough **I**mproving **C**ontractility in **H**eart **F**ailure), the Phase 3 clinical trial evaluating *omecamtiv mecarbil* in patients with heart failure with reduced ejection fraction (HFrEF), were presented by Dr. John Teerlink, M.D., Professor of Medicine, University of California San Francisco, Director of Heart Failure, San Francisco Veterans Affairs Medical Center and Executive Committee Chair, GALACTIC-HF, at the American Heart Association (AHA) Scientific Sessions 2021.

In addition, preclinical data were presented at the AHA Scientific Sessions by Ivan Luptak, M.D., Ph.D., Assistant Professor of Medicine, Boston University School of Medicine, on a closely related analog to CK-3828136 (CK-136), the company's novel, selective cardiac troponin activator which is in development for the potential treatment of diseases associated with impaired cardiac contractility, such as HFrEF, right ventricular heart failure, and others.

"The results from this post-hoc analysis from GALACTIC-HF showed that treatment with *omecamtiv mecarbil* significantly reduced the risk of stroke, a common comorbidity in patients with HFrEF, in addition to its previously demonstrated effect having met its primary composite endpoint of time to first heart failure event or cardiovascular death. Reducing stroke may be an important additional benefit to treatment with *omecamtiv mecarbil* in patients with HFrEF, many of whom are at high risk of having a stroke or have a history of stroke," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President of Research & Development. "Additionally, the new data presented at AHA on a closely related analog to the cardiac troponin activator, CK-136, adds preclinical evidence that directly targeting the sarcomere through this novel mechanism may increase cardiac contractility without a negative impact on calcium cycling, diastolic function or contractile reserve and thereby may improve performance without impacting cardiac efficiency."

Treatment with *Omecamtiv Mecarbil* Associated with Significant Reduction in Risk of Stroke in GALACTIC-HF

Additional analyses presented from GALACTIC-HF focused on the effect of treatment with *omecamtiv mecarbil* on the risk of stroke in patients with heart failure with reduced ejection fraction (HFrEF). Among patients enrolled in the trial, 754 (9.2%) had a history of stroke. These patients were older, more likely to be non-white, and were more likely to have atrial fibrillation/flutter, hypertension, diabetes mellitus, ischemic heart disease, worse New York Heart Association (NYHA) functional class, and higher baseline NT-proBNP or troponin compared to patients with no history of stroke. A total of 194 non-fatal and fatal strokes were reported in GALACTIC-HF. Multivariate predictors of the incidence of first stroke in GALACTIC-HF included non-white race, history of stroke or percutaneous coronary intervention, and elevated baseline troponin or systolic blood pressure. The treatment effect of *omecamtiv mecarbil* on the primary composite endpoint of cardiovascular death or heart failure events was similar in patients with a history of stroke (hazard ratio 0.86; 95% confidence interval (CI) 0.70, 1.07; p=0.18) and in patients without a history of stroke (hazard ratio 0.93; 95% CI 0.87, 1.00; p=0.06; interaction p-value=0.40). However, among all patients who received *omecamtiv mecarbil*, the risk of first fatal or non-fatal stroke was reduced by 35% (hazard ratio 0.65; 95% CI 0.49, 0.87; p=0.004), and the risk of fatal stroke was reduced by 44% (hazard ratio 0.56; 95% CI 0.31, 0.99; p=0.048). Treatment with *omecamtiv mecarbil* was associated with greater reductions in stroke for patients with a history of stroke, reducing the risk by 77% (n=754, hazard ratio 0.23; 95% CI 0.09, 0.56; interaction p-value=0.001), as well as in patients with a history of atrial fibrillation, reducing the risk by 51% (n=3475, hazard ratio 0.49, CI 0.32, 0.76; p=0.001). Treatment with *omecamtiv mecarbil* also demonstrated a reduction in new onset atrial fibrillation/flutter (no atrial fibrillation/flutter present at screening: n=5987, hazard ratio 0.70, CI 0.50, 0.99; p=0.044; no history of atrial fibrillation/flutter: n=4757, hazard ratio 0.60, CI 0.37, 1.00; p=0.048). This reduction in stroke may be related to the reduction in adverse events of atrial fibrillation/flutter, as well as improvements in atrial and ventricular function that have been observed in GALACTIC-HF and previous clinical trials of *omecamtiv mecarbil*. These findings may have implications for the clinical impact of *omecamtiv mecarbil* and suggest that it has a potential added benefit of decreasing the risk of stroke in patients with HFrEF.

Cardiac Troponin Activator Increases Contractility Without Negative Impacts on Myocardial Energetics

New preclinical data investigated the effects on cardiac contractility and energetics on a closely related analog to CK-136, a cardiac troponin activator referred to as TA1. Several *in vitro, ex vivo* and *in vivo* studies demonstrated that TA1 increased myocardial contractility by sensitizing the sarcomere to calcium without impairing diastolic function or depleting the cardiac energy reserve. In bovine cardiac myofibrils and human cardiac microtissues, TA1 increased the calcium sensitivity of sarcomere function dose dependently. Similarly, TA1 increased calcium sensitivity and maximal tension *ex vivo* in mouse cardiac fibers, and in anesthetized normal rats, TA1 also dose dependently increased fractional shortening, a measure of cardiac contractility. Finally, assessments of isolated perfused rat hearts by 31P NMR spectroscopy comparing TA1 to dobutamine, a calcitrope that increases cardiac output, both TA1 and dobutamine similarly increased rate pressure product, but unlike dobutamine, TA1 did not worsen cardiac energetics, elevate left ventricular end-diastolic pressure (LVEDP) or raise heart rate. Magnetization transfer experiments also confirmed that the higher force generation from TA1 did not come at a cost of higher ATP consumption, as compared to dobutamine. Together, these data suggest that cardiac troponin activation increases cardiac contractility without causing a negative impact on calcium cycling, diastolic function or contractile reserve. Because energy depletion has been associated with worse long-term survival in heart failure, these results suggest cardiac troponin activation may have application in diseases associated with decreased cardiac contractility. These findings were also published online in *Circulation: Heart Failure*[1] in conjunction with their presentation.

About *Omecamtiv Mecarbil*

Omecamtiv mecarbil is an investigational, selective, small molecule cardiac myosin activator, the first of a novel class of myotropes[1] designed to directly target the contractile mechanisms of the heart, binding to and recruiting more cardiac myosin heads to interact with actin during systole. *Omecamtiv mecarbil* was designed to increase the number of active actin-myosin cross bridges during each cardiac cycle and consequently augment the impaired contractility that is associated with heart failure with reduced ejection fraction. Preclinical research has shown that *omecamtiv mecarbil*

increases cardiac contractility without increasing intracellular myocyte calcium concentrations or myocardial oxygen consumption.[2-4]

The development program for *omecamtiv mecarbil* is assessing its potential for the treatment of HFrEF and includes GALACTIC-HF and METEORIC-HF, a Phase 3 clinical trial designed to evaluate the effect of treatment with *omecamtiv mecarbil* compared to placebo on exercise capacity.

About CK-136

CK-136 is an investigational, selective, small molecule cardiac troponin activator. In preclinical models, CK-136 increases myocardial contractility by binding to cardiac troponin through an allosteric mechanism that sensitizes the cardiac sarcomere to calcium, facilitating more actin-myosin cross bridge formation during each cardiac cycle, thereby resulting in increased myocardial contractility. Similar to cardiac myosin activation, preclinical research has shown that cardiac troponin activation does not change the calcium transient of cardiac myocytes. The development program for CK-136 is assessing its potential for the treatment of diseases associated with impaired cardiac contractility, such as heart failure with reduced ejection fraction (HFrEF), right ventricular heart failure, and others.

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. 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 preparing a U.S. NDA submission of *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 *aficamten*, a next-generation cardiac myosin inhibitor, for the potential treatment of hypertrophic cardiomyopathies (HCM). The company has announced positive results from Cohorts 1 and 2 in REDWOOD-HCM, a Phase 2 clinical trial of *aficamten* in patients with obstructive HCM. Cytokinetics is conducting start-up activities for SEQUOIA-HCM, the Phase 3 clinical trial of *aficamten* in patients with obstructive HCM. Cytokinetics is also developing *reldesemtiv*, a fast skeletal muscle troponin activator, currently the subject of COURAGE-ALS, a Phase 3 clinical trial in patients with 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 potential benefits of *omecamtiv mecarbil*, *aficamten* or CK-136, statements relating to the potential submission or approval of an NDA for *omecamtiv mecarbil*, statements relating to the timing of a potential commercial launch of *omecamtiv mecarbil*, and statements relating to the timing of the commencement or completion of the SEQUOIA-HCM clinical trial. Cytokinetics' research and development activities; the design, timing, results, significance and utility of preclinical and clinical results; and the properties and potential benefits of Cytokinetics' other 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; Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy; the FDA or foreign regulatory agencies may delay or limit Cytokinetics' ability to conduct clinical trials; Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; standards of care may change, rendering Cytokinetics' drug candidates obsolete; and competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target. 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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