



Intra-Cellular Therapies Announces Publications Highlighting Beneficial Effects of Phosphodiesterase Type I Inhibition with Lenrispodun (ITI-214) on Cardiovascular Function in Patients with Heart Failure and in Models of Accelerated Aging

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Results of Study ITI-214-104 show that lenrispodun, in a Phase 1/2a Study, is well tolerated and acts as an inodilator in patients with heart failure without inducing abnormal heart rhythms (Circulation: Heart Failure; Gilotra, et al, 2021)

A novel cellular mechanism has been identified by which lenrispodun promotes cardiomyocyte contraction, offering a potential effective and safer alternative for the treatment of heart failure (Circulation Research; Muller, et al, 2021)

In two additional recent studies using genetic models of accelerated aging, lenrispodun was shown to ameliorate arteriopathy associated with aging (Journal of Pharmacology and Experimental Therapeutics; Golshiri et al. 2021; and Oxidative Medicine and Cellular Longevity; Ataabadi, et al, 2021)

These findings further define the mechanism of action and potential therapeutic utility of PDE1 inhibitors for several conditions, including diseases where inflammation plays a role, such as Parkinson's disease and indications where the cardiovascular system may be affected

NEW YORK, Sept. 20, 2021 (GLOBE NEWSWIRE) -- Intra-Cellular Therapies, Inc. (Nasdaq: ITCI) today highlights the publication of four manuscripts that report on the mechanism of action of lenrispodun (ITI-214) and the potential cardiovascular therapeutic effects of Phosphodiesterase Type I (PDE1) inhibition.

"PDE1 inhibition restores intracellular signaling by elevating the second messengers cAMP and cGMP in certain pathological states associated with low levels of these signaling molecules. PDE1 enzymes require calcium and calmodulin for their activation and are expressed in multiple tissues including smooth and cardiac muscle, neurons, and macrophages/microglia providing opportunities to treat multiple diseases," said Robert Davis, PhD, Senior Vice President and Chief Scientific Officer, Intra-Cellular Therapies. "The findings highlighted today describe beneficial effects of lenrispodun in the treatment of patients with heart failure, and in age-related vascular changes in preclinical models associated with stiffening of arteries, vascular endothelial dysfunction, and increased inflammation. Vascular dysfunction is an important risk factor for cardiovascular disease. In addition, a novel cellular mechanism has been identified by which PDE1 stimulates cardiac contraction. These findings have broad implications as cardiovascular dysfunction and inflammation play important roles across multiple chronic and age-related human diseases."

The first manuscript entitled "Acute Hemodynamic Effects and Tolerability of Phosphodiesterase-1 Inhibition With ITI-214 in Human Systolic Heart Failure" was published online in *Circulation: Heart Failure* (Gilotra, et al, 2021).

This manuscript reports on the findings of study ITI-214-104. This was the first study of a PDE1 inhibitor (lenrispodun, ITI-214) in patients with heart failure with reduced ejection fraction (HFrEF). Acute, single oral doses of lenrispodun (30 or 90 mg) increased mean left ventricular power index, cardiac output and heart rate while inducing systemic arterial vasodilation. Importantly, lenrispodun was well-tolerated in these patients. The hemodynamic profile of acute lenrispodun in humans was analogous to that reported in our animal preclinical studies (Hashimoto, et al., 2018). Topline data from this study has previously been presented.

The second manuscript entitled "PDE1 inhibition modulates Cav1.2 channel to stimulate cardiomyocyte contraction" was published online in *Journal Circulation Research* (Muller, et al, 2021).

This manuscript describes studies in cardiomyocytes that express the PDE1C isoform, the predominant isoform in human heart, and elucidates a mechanism by which lenrispodun increases cardiac contractility. New findings in this study reveal that the action of lenrispodun, our PDE1 inhibitor, improves cardiac contractility by activating protein kinase A, results in increased L-type calcium channel conductance but does not require changes in other intracellular calcium stores (e.g., sarcoplasmic reticulum).

The findings of these two studies indicate that PDE1 inhibition caused by lenrispodun may provide a positive inotropic therapy for heart failure which is mediated by a novel mechanism of action.

The third manuscript entitled "Selective PDE1 inhibition ameliorates vascular function, reduces inflammatory response, and lowers blood pressure in ageing animals" was published online in the *Journal of Pharmacology and Experimental Therapeutics* (Golshiri et al. 2021).

This manuscript describes the acute and chronic effects of PDE1 inhibition using lenrispodun on prominent aging related changes in macro- and micro- circulation and inflammatory status in a mouse model of accelerated aging involving a genetic deletion yielding a reduction in the activity of the DNA repair enzyme, ERCC1 (excision repair cross complement 1) endonuclease (Ercc1Δ/- mice). This accelerated aging model enables pharmacotherapy during the entire course of the aging process. This study showed that lenrispodun treatment reduced age-related elevated vasoconstriction of the aorta, and coronary arteries, and as a consequence increased blood flow in the microcirculation in these mice. In addition, lenrispodun reduced cardiac hypertrophy and levels of pro-inflammatory but not anti-inflammatory cytokines in this model.

The fourth manuscript entitled "Vascular Ageing Features Caused by Selective DNA Damage in Smooth Muscle Cell." was published online in *Oxidative Medicine and Cellular Longevity* (Ataabadi, et al, 2021).

This manuscript describes studies using a model of accelerated aging similar to the one described above but where the activity of the Ercc1 enzyme was selectively knocked out only in smooth muscle (SMC) and not in the entire body. These SMC- Ercc1 Δ /- mice show a progressive aging phenotype in resistant and conduit arteries. Importantly, PDE1 inhibition by lenrispodun normalizes vasodilator function in progressive vascular smooth muscle dysfunction in this mouse model.

Stiffening of arteries, vascular endothelial dysfunction, and increased inflammation may represent important risk factors for cardiovascular disease. The ability of lenrispodun to ameliorate these deficits, if translated to humans, suggests a potential therapeutic utility in treating arteriopathy associated with aging.

Phosphodiesterase type 1 (PDE1) inhibitor Portfolio

Our PDE1 inhibitor program is focused on diseases in which the PDE1 enzyme is over-expressed and/or abnormal immune cell function contributes to disease pathology providing opportunities to pursue innovative treatments for multiple diseases including Parkinson's disease, heart failure and other diseases including cancer.

Lenrispodun is a potent and selective PDE1 Inhibitor and is the lead compound in the Company's PDE1 portfolio. Lenrispodun works by blocking the breakdown of cyclic nucleotides (cAMP, cGMP), thus allowing these molecules to build up in the cells and to exert important functions. Lenrispodun has been generally well tolerated with a favorable safety profile in eight Phase 1/2a clinical trials. Lenrispodun is in clinical development for the treatment of symptoms associated with Parkinson's disease and for the treatment of heart failure.

Previous studies have described the mechanism of action of lenrispodun in the brain. The mechanism of action of lenrispodun and our other PDE1 inhibitors suggests therapeutic potential across a variety of diseases including neurological and cardiovascular diseases and cancer.

About Intra-Cellular Therapies

Intra-Cellular Therapies is a biopharmaceutical company founded on Nobel prize-winning research that allows us to understand how therapies affect the inner-workings of cells in the body. The company leverages this intracellular approach to develop innovative treatments for people living with complex psychiatric and neurologic diseases. For more information, please visit www.intracellulartherapies.com.

Forward-Looking Statements

This news release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, the therapeutic value, clinical and non-clinical development plans and commercial potential of our drug product candidates; the progress, timing and results of our clinical trials and preclinical studies; our beliefs about the extent to which the results of our clinical trials and preclinical studies to date support new drug application filings for product candidates; the safety and efficacy of our product development candidates; our beliefs about the potential uses and benefits of our drug product candidates; the potential for ITI-214 to represent a novel approach for the treatment of human heart failure; that ITI-214 offers a potential new treatment for heart failure with a novel mechanism of action that may provide an effective and safer alternative to existing therapies and development efforts and plans under the caption "About Intra-Cellular Therapies." All such forward-looking statements are based on management's present expectations and are subject to certain factors, risks and uncertainties that may cause actual results, outcome of events, timing and performance to differ materially from those expressed or implied by such statements. These risks and uncertainties include but are not limited to the following: our current and planned clinical trials, other studies for our product candidates may not be successful or may take longer and be more costly than anticipated; product candidates that appeared promising in earlier research and clinical trials may not demonstrate safety and/or efficacy in larger-scale or later clinical trials; our proposals with respect to the regulatory path for our product candidates may not be acceptable to the FDA; our reliance on collaborative partners and other third parties for development of our product candidates; the COVID-19 pandemic may negatively impact the conduct of, and the timing of enrollment, completion and reporting with respect to, our clinical trials; any other impacts on our business as a result of or related to the COVID-19 pandemic; and the other risk factors detailed in our public filings with the Securities and Exchange Commission. All statements contained in this press release are made only as of the date of this press release, and we do not intend to update this information unless required by law.

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