Celladon Corporation Announces Pre-clinical Study Demonstrating Inhalable MYDICAR Reverses Pulmonary Arterial Hypertension (PAH)

-MYDICAR When Inhaled May Restore Function of SERCA2a Enzyme in the Lungs to Reverse Deadly PAH Condition-

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San Diego, California, July 30, 2013/PRNewswire/ -- Celladon Corporation, a clinical-stage biotechnology company committed to applying its first-mover, leadership position in the field of SERCA enzymes to transform the lives of patients with important, life-threatening diseases, announced today that an international team of researchers led by investigators at the Cardiovascular Research Center at Icahn School of Medicine at Mount Sinai demonstrate that the deadly condition known as pulmonary arterial hypertension (PAH), which afflicts up to 150,000 Americans each year, may be reversible by using an inhalable form of Celladon's gene therapy product candidate MYDICAR (AAV1/ SERCA2a).

In their new study, reported in the July 30 issue of the journal Circulation, scientists demonstrated that MYDICAR administered through a nebulizer-like inhalation device can completely reverse PAH in rat models of the disease. In the lab, researchers also showed in pulmonary artery PAH patient tissue samples reduced expression of the SERCA2a, an enzyme critical for proper pumping of calcium in calcium compartments within the cells. MYDICAR could therefore be sought as a promising therapeutic intervention in PAH.

Krisztina Zsebo Ph.D., President and CEO of Celladon Corp and a co-author of the study said "Gene therapy represents an entirely new therapeutic modality for the treatment of PAH. We are very excited about the potential of using MYDICAR for this purpose. There is a tremendous need for new treatment options in PAH and we look forward to conducting additional studies investigating the potential benefit of MYDICAR in this patient population'

"The MYDICAR gene therapy could be delivered very easily to patients through simple inhalation — just like the way nebulizers work to treat asthma," says study co-senior investigator Roger J. Hajjar, MD, Director of the Cardiovascular Research Center and the Arthur & Janet C. Ross Professor of Medicine and Professor of Gene & Cell at Icahn School of Medicine at Mount Sinai. "We are excited about testing this therapy in PAH patients who are in critical need of intervention."

This same SERCA2a dysfunction also occurs in heart failure. This new study utilizes Celladon's product candidate MYDICAR which is currently under investigation in an international 200 patient Phase IIb trial in the United States and Europe. In 2012, Celladon and the Mt. Sinai School of Medicine entered into a license agreement granting Celladon certain exclusive worldwide rights to develop and commercialize SERCA2a gene therapy products for PAH.

"What we have shown is that gene therapy restores function of this crucial SERCA2a enzyme in diseased lungs," says Dr. Hajjar. "We are delighted with these new findings because it suggests that MYDICAR which is already showing great benefit in congestive heart failure patients may be able to help PAH patients who currently have no good treatment options — and are in critical need of a life sustaining therapy."

When SERCA2a is down-regulated, calcium stays longer in the cells than it should, and it induces pathways that lead to overgrowth of new and enlarged cells. According to researchers, the delivery of the SERCA2a gene through the MYDICAR product in turn produces SERCA2a enzymes, which helps both heart and lung cells restore their proper use of calcium.

“We are now on a path toward PAH patient clinical trials in the near future,” says Dr. Hajjar, a co-founder of Celladon who developed the gene therapy approach. Studies in large animal models are now underway. SERCA2a gene therapy has already been approved by the National Institutes of Health for human study.

A Simple MYDICAR Inhalation Corrects Deadly Dysfunction

PAH most commonly results from heart failure in the left side of the heart or from a pulmonary embolism, when clots in the legs travel to the lungs and cause blockages. When the lung is damaged from these conditions, the tissue starts to quickly produce new and enlarged cells, which narrows pulmonary arteries. This increases the pressure inside them. The high pressure in these arteries resists the heart’s effort to pump through them and the blood flow between the heart and lungs is reduced. The right side of the heart then must overcome the resistance and work harder to push the blood through the pulmonary arteries into the lungs. Over time, the right ventricle becomes thickened and enlarged and heart failure develops.

The MYDICAR gene therapy that Dr. Hajjar developed uses a modified adeno-associated viral-vector (AAV-vector). It works by introducing a healthy SERCA2a gene into cells, but this gene does not incorporate into a patient’s chromosome, according to the study’s lead author, Lahouaria Hadri, PhD, an Instructor of Medicine in Cardiology at Icahn School of Medicine at Mount Sinai. “The clinical trials in congestive heart failure have shown already that the gene therapy is very safe,” says Dr. Hadri.

The clinical application of MYDICAR for patients with PAH will differ from those with heart failure. When treating heart failure patients, MYDICAR is infused through the coronary arteries of heart failure patients using catheters, while in PAH patients, MYDICAR will need to be administered through inhalation.

This study was supported by National Institutes of Health grants (K01HL103176, K08111207, R01 HL078691, HL057263, HL071763, HL080498, HL083156, and R01 HL105301).

About MYDICAR in Heart Failure

MYDICAR is a genetically targeted enzyme replacement therapy intended to restore levels of SERCA2a, a regulator of calcium cycling in the heart and cardiac contractility. SERCA2a levels decline in all forms of late-stage HF resulting in deficient heart function. With MYDICAR, the SERCA2a gene is delivered using recombinant adeno-associated virus (AAV) as the vector. AAV is a naturally occurring virus not associated with any disease in humans. MYDICAR is delivered in a single dose directly to the heart during a routine outpatient cardiac catheterization procedure, similar to an angiogram. MYDICAR is synergistic and additive across current HF treatments such as ACE inhibitors, beta-blockers, sprinolactone/diuretics, and biventricular pacing devices. No treatment substitution decision is required by the treating physician. A recent Phase 2 clinical trial demonstrated sustained improvement at one year in cardiac function parameters and quality of life. A 200 patient Phase 2b study of MYDICAR was initiated in August, 2012

About the CUPID Phase 2b Trial in Heart Failure

The CUPID Phase 2b trial was initiated in August 2012 and will enroll approximately 200 patients in up to 50 sites worldwide. Patients will first be prescreened for the presence of AAV neutralizing antibodies. Those patients with a negative titer will undergo further screening tests and procedures to determine eligibility prior to randomization and enrollment into the study. All patients will be randomized in parallel to MYDICAR or placebo in a ratio of 1:1 (1×10^{13} DRP MYDICAR to placebo).

The primary objective is to determine the efficacy of MYDICAR in patients with ischemic or dilated cardiomyopathy and NYHA class II/IV symptoms of HF by reducing the frequency and/or delaying HF-related hospitalizations compared to placebo-treated patients.

The primary efficacy endpoint is time-to-recurrent HF-related hospitalizations in the presence of terminal events (all-cause death, heart transplant, LVAD implantation). The secondary efficacy endpoint is the time-to-terminal event (all-cause death, heart transplant, LVAD implantation). Exploratory endpoints include change from baseline in NYHA class, 6 minute walk test distance, and quality of life (KCCQ) score.

Secondary objectives will include assessment of the safety of MYDICAR by determining the incidence and severity of adverse events and changes in laboratory parameters. Safety evaluations include the incidence and severity of all adverse events (including procedure-related), summaries of concomitant medications, vital signs, physical exams, implantable cardioverter defibrillator (ICD) interrogations and laboratory parameters, and the time to cardiovascular-related death.

About Celladon

Celladon is a privately held clinical stage biotechnology company committed to applying our first-mover, leadership position in the field of SERCA enzymes to transform the lives of patients with important, life-threatening diseases. SERCA's are a family of enzymes relevant to regulating intra-cellular calcium in all human cells. In turn, cellular calcium levels and calcium dysregulation plays a crucial role in a number of important and complex medical conditions and diseases such as heart failure, PAH, diabetes and Alzheimer's disease. Our singular focus is to apply our scientific leadership position to develop gene therapies and small molecules for these complications and we believe Celladon is a first mover in this emerging field. Our lead development program MYDICAR is currently under investigation in an international 200 patient Phase 2b clinical trial in advanced heart failure.
Further information can be found at www.celladon.net.

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