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Cardiorenal Actions of Trevena Biased Ligand Heart Failure Drug Explained in Mayo Clinic Publication and Presentations

Pharmacology studies of TRV027, a β-arrestin biased AT1R ligand, in an experimental heart failure dog model, are published in CIRC:Heart Failure and presented at two heart failure meetings this month

KING OF PRUSSIA, Pa.--(BUSINESS WIRE)-- Trevena, Inc., the leader in the discovery of G-protein coupled receptor (GPCR) biased ligands, announced today that key translational pharmacology studies of its lead molecule TRV027 were published on August 11th, 2011 in *Circulation:Heart Failure*, and that new data from another of these studies were presented at The European Society of Cardiology meeting in Paris on August 31st, 2011. Additional data on the compound will also be presented as a poster at the upcoming Heart Failure Society of America meeting in Boston, on September 19th.

TRV027, a novel injectable agent being developed by Trevena to treat acute heart failure, showed promising results in a series of studies designed to test potential clinical benefits of the drug. In these studies TRV027 successfully and reproducibly ameliorated measures of acute heart failure in a well-validated canine model of the disease. These findings resulted from a multi-year collaboration with John C. Burnett, Jr, MD and Guido Boerritger, MD of Mayo Clinic.

The data published this month in *Circulation:Heart Failure* shows that TRV027 rapidly and reversibly corrects hemodynamic parameters altered in paced heart failure canines, including both vascular and cardiac measures, while preserving renal function. These same parameters are key measures of clinical benefit in acute heart failure. The article is entitled “Cardiorenal Actions of TRV120027, a Novel, β-Arrestin Biased Ligand at the Angiotensin II Type 1 Receptor, in Healthy and Heart Failure Canines: A Novel Therapeutic Strategy for Acute Heart Failure” (PMID: 21835984). In these studies, TRV027 increased cardiac output while decreasing pulmonary capillary wedge pressure and systemic and renal vascular resistances in a dose dependent manner. These hemodynamic changes were achieved with a concurrent increase in renal blood flow, and maintenance of glomerular filtration rate and urinary sodium excretion in paced heart failure canines, which typically exhibit significant drops in these renal parameters.

Those findings were further extended in data from another dog model study presented at the ESC meeting in Paris on August 31st. These and additional data on compound mechanism will also be shown at HFSA later this month. This most recent study demonstrates that the pharmacologic effects of TRV027 are preserved when administered with the diuretic furosemide, which is currently first-line therapy for acute heart failure. The two drugs worked safely together in the paced canine model of heart failure to provide rapid, titratable

correction of hemodynamic and renal measures.

These experiments represent successful translation of TRV027 from *in vitro* and rodent studies (published in JPET in 2010 – PMID 20801892), to a robust model of human disease, and provide a solid platform for clinical development. The dog study findings also provide key insight into how TRV027 may provide therapeutic benefit in clinically relevant settings. TRV027 is currently in a randomized, placebo-controlled, double-blind, dose-ranging phase 2a clinical study. This study will assess the hemodynamic effects of TRV027 in patients with stable heart failure, and aims to demonstrate that TRV027 rapidly and predictably improves hemodynamics while improving cardiac output and protecting renal function as seen in preclinical species. In patients suffering from acute heart failure, these titratable pharmacologic effects are expected to result in rapid symptom improvement.

About Acute Heart Failure

AHF represents a serious challenge for patients, physicians and healthcare systems. The American Heart Association estimated that heart failure cost the U.S. healthcare system more than $38 billion in 2008, including direct hospital costs of $20 billion. AHF is already the leading reason for hospitalization of individuals over 65 years old in the United States, with an estimated 1.5 million admissions last year, and is the most costly diagnosis for Medicare. Despite the significance of this problem, current therapies are not producing meaningful improvements in patient outcomes. AHF incidence is increasing unchecked, and both heart failure mortality and hospital re-admission following an AHF event remain extremely high. For all of these reasons, there is an urgent need for better treatments, and a clear incentive for regulators and payers to approve and reimburse them.

About Trevena and Biased Ligands

Trevena, Inc. is a clinical stage pharmaceutical company focused on discovering and developing the next generation of G-protein coupled receptor (GPCR) targeted medicines. GPCRs are the targets for at least one-third of modern medicinal products, and they remain the predominant class of targets under clinical evaluation. Despite the past success of GPCR drugs, there is a significant opportunity to enhance the therapeutic properties of these molecules by specifically activating selected receptor signals. Trevena's expertise lies in understanding which signaling pathways downstream of a GPCR are associated with beneficial versus adverse biological effects, and in engineering "biased ligands" that activate only the beneficial pathways to unlock new biology and avoid drug adverse effects. This approach builds on extensive research from the laboratories of leading scientists in the GPCR field - Robert Lefkowitz, M.D. and Howard Rockman, M.D., at the Duke University Medical Center. Trevena's platform can be broadly applied across therapeutic areas and its pipeline currently includes programs in cardiovascular and CNS diseases. Founded in 2008, Trevena is based in King of Prussia, Pennsylvania and is a privately held company backed by leading investors including Alta Partners, Healthcare Ventures, NEA, Polaris and Yasuda Enterprise Development Company. For more information about the company, please visit www.trevenainc.com.

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