European Respiratory Society
Annual Congress 2012

Abstract Number: 2768

Publication Number: 3274

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** No keyword **Keyword 3:** No keyword

Title: Cicletanine in pulmonary arterial hypertension (PAH): Results from a phase 2 randomized placebo-controlled trial

Dr. Aaron 7205 Waxman abwaxman@partners.org MD [1], Dr. Ronald 22483 Oudiz ROudiz@LABiomed.org MD [2], Dr. Shelley 22489 Shapiro Shelley.Shapiro@va.gov MD [3], Dr. Mardi 22490 Gomberg-Maitland mgomberg@medicine.bsd.uchicago.edu MD [4], Dr. Anne 22493 Keogh amkeogh@stvincents.com.au MD [5], Dr. David 22495 Badesch David.Badesch@uchsc.edu MD [6], Dr. Robert 22496 Frantz frantz.robert@mayo.edu MD [7], Dr. C. Gregory 22499 Elliott greg.elliott@imail.org MD [8], Dr. Hunter 22500 Gillies Hunter.Gillies@gilead.com MD [9] and Dr. Gennyne 22501 Walker Gennyne.Walker@gilead.com [9]. [1] Department of Medicine, Pulmonary and Critical Care, Brigham and Women's Hospital, Boston, MA, United States, 02115 ; [2] Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, United States, 90502 ; [3] Department of Cardiology, West Los Angeles VA HealthCare Center, Los Angeles, CA, United States, 90073 ; [4] Department of Medicine, Pulmonary Hypertension Center, Univeristy of Chicago, IL, United States, 60637 ; [5] Heart Failure and Transplant Unit, St. Vincent's Hospital, Sydney, NSW, Australia, 2010 ; [6] Divisions of Pulmonary Sciences and Critical Care Medicine, and Cardiology, University of Colorado, Denver, CO, United States, 80045 ; [7] Division of Cardiovascular Disease, Mayo Clinic, Rochester, MN, United States, 55905 ; [8] Department of Medicine, Intermountain Medical Center and The University of Utah, Murray, UT, United States, 84157 and [9] Cardiovascular Clinical Research, Gilead Sciences, Inc., Foster City, CA, United States, 94404 .

Body: Cicletanine (CIC) is an antihypertensive with vasorelaxant and diuretic properties. Potential efficacy was observed with compassionate use of CIC in worsening PAH. A controlled study investigating the safety and efficacy of CIC for PAH was performed. 162 subjects were randomized to 12 weeks of placebo (n=41) or CIC at doses of 150 mg qd (n=39), 150 mg bid (n=40) or 300 mg qd (n=42). Subjects could be on stable doses of an endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, parenteral prostanoid, or any 2-drug combination. The primary analysis was comparison of change in 6-minute walk distance (6MWD) following 12 weeks of treatment with daily doses of CIC 300 mg (150 mg bid+300 mg qd; n=80) to placebo. Secondary analyses included dyspnea, WHO functional class, NT-proBNP, and a subset analysis of pulmonary hemodynamics (n=50). 57.4% of subjects had idiopathic PAH and 42.6% associated PAH; 38.9% of subjects were WHO Class II, 61.1% WHO Class III and the mean baseline 6MWD was 370±64 meters (m). For the 300 mg combined group (n=80), the placebo-adjusted mean and median changes from baseline in 6MWD were +19.4 m (95% CI: 0.3, 38.4) and +7.0 m (95%: CI -8.0, 24.0), respectively (p=0.50). There were no clinically relevant improvements in the secondary assessments, including pulmonary vascular resistance (mean change 35 dyne·s/cm5). The adverse events reported more frequently with CIC

were nausea, hypokalemia, and fatigue, consistent with known properties of diuretics. Although CIC was generally well-tolerated, no improvements in exercise tolerance, symptoms or hemodynamics were observed in patients with PAH after 12 weeks of CIC treatment.