



Ironwood Presents Praliciguat Phase IIa Study Data Showing Positive Impact on Metabolic and Cardiovascular Clinical Endpoints at the American Diabetes Association's 78th Scientific Sessions

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– Data provide additional evidence supporting development of praliciguat as a potential treatment for diabetic nephropathy and for heart failure with preserved ejection fraction –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 23, 2018-- [Ironwood Pharmaceuticals, Inc.](#) (NASDAQ: IRWD), a commercial biotech company, today presented additional data from an exploratory Phase IIa study of praliciguat (IW-1973) in patients with type 2 diabetes and hypertension during an oral session at the American Diabetes Association's (ADA) 78th Scientific Sessions in Orlando, Fla. Praliciguat is an oral, once-daily soluble guanylate cyclase (sGC) stimulator that is currently being studied in Phase II clinical trials in patients with diabetic nephropathy and in patients with heart failure with preserved ejection fraction (HFpEF).

Building on [previously announced top-line data](#) from the Phase IIa randomized, placebo-controlled, 14-day study, which showed that treatment with praliciguat led to reductions in blood pressure, fasting plasma glucose, cholesterol levels and triglycerides in patients on a stable regimen of medicines to manage their disease, the newly reported findings also suggested that praliciguat improved insulin sensitivity. Insulin resistance is a hallmark of diabetes¹ and often linked to hypertension². In addition, the data suggested that praliciguat decreased levels of apolipoprotein B (ApoB), a key lipid parameter that – when elevated – is associated with increased cardiac events³. The effect of praliciguat on ApoB in this Phase IIa study was shown within the context of broader lipid effects, including a reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol, the component of total cholesterol associated with long-term cardiovascular risk.

"In this study, praliciguat demonstrated a positive impact across critical biomarkers of metabolic and cardiovascular disease – including blood pressure, lipids, and glucose – providing a strong rationale for praliciguat as a potential treatment for diabetic nephropathy and for HFpEF," said Christopher Wright, M.D., Ph.D., senior vice president, global development and chief development officer at Ironwood. "We're advancing our Phase II programs for these diseases, which both impact millions of patients worldwide, have limited treatment options and are associated with serious long-term consequences including organ failure and death."

The newly disclosed data presented at the ADA Scientific Sessions were as follows:

- **Improvement in insulin sensitivity:** In patients treated with praliciguat who were not taking concomitant insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score – a measure of insulin resistance – declined by an average of 36% from baseline to day 15, following completion of the study treatment regimen, compared to a decrease of 13% in patients taking placebo, representing a 23% greater reduction with praliciguat compared to placebo.
- **Decline in ApoB:** Patients treated with praliciguat showed a mean decrease in ApoB of 170 mcg/ml from baseline to day 15, compared to a decrease of 51 mcg/ml in patients taking placebo, a 119 mcg/ml greater reduction with praliciguat compared to placebo.

The Phase IIa exploratory study was designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of praliciguat in diabetic patients with hypertension, and included a number of exploratory biomarkers related to diabetes and cardiovascular disease. The study included two active dosing regimens: (1) 40 mg once-daily for days 1 to 14, and (2) 20 mg twice daily for days 1 to 7 followed by 40 mg once daily for days 8 to 14. Overall, results were similar for both dosing regimens, and data were combined for analysis.

The study was not designed or powered to assess efficacy, but the data yielded clear and consistent trends indicating a positive effect of praliciguat on blood pressure, metabolic parameters and endothelial function biomarkers. These improvements were seen in patients who were taking a stable regimen of therapies to manage their disease; all participating patients were taking at least one medication to manage their hypertension and at least one medication to manage their diabetes, and a majority were also taking additional medications to manage their cholesterol and serum lipid levels. The study also confirmed a pharmacokinetic profile of praliciguat supporting once-daily dosing and suggested broad distribution to relevant tissues, offering the potential to maximize anti-inflammatory, anti-fibrotic and metabolic effects.

Praliciguat was generally well-tolerated. Nausea was the only adverse event (AE) present in the praliciguat group at a greater incidence rate than placebo. There was a single serious AE, an upper gastrointestinal hemorrhage in a participant with erosive esophagitis receiving praliciguat. Across all five clinical studies of praliciguat to date, praliciguat was found not to impair platelet function or blood clotting, either on its own or when co-administered with aspirin. No other serious bleeding episodes have been observed. All other AEs in this Phase IIa study were characterized as mild.

About Praliciguat

Praliciguat (IW-1973), an oral, once-daily soluble guanylate cyclase (sGC) stimulator, is being studied in patients with diabetic nephropathy and in patients with heart failure with preserved ejection fraction (HFpEF). Diabetic nephropathy affects an estimated eight million Americans and 20 to 40 percent of all diabetic patients worldwide. It is the leading cause of end-stage renal disease. Currently available products do not treat the underlying pathophysiology of the disease or fully address the needs of this patient population. HFpEF affects an estimated three million Americans and 40 to 70

percent of heart failure patients worldwide. It is a highly symptomatic condition with high rates of morbidity and mortality that can cause insufficient delivery of oxygen to the tissues, fluid in the lungs and edema of the extremities, causing patients to be short of breath and have compromised exercise tolerance. There are no approved therapies to treat HFpEF.

Currently in Phase II development for diabetic nephropathy and for HFpEF, praliciguat has the potential to address the underlying causes of these devastating diseases by improving nitric oxide (NO) signaling, which may improve vascular and metabolic function and decrease the inflammatory and fibrotic consequences associated with these diseases.

About Ironwood's sGC Program

As a pioneering expert in cyclic GMP (cGMP), Ironwood is building on its success with linaclotide, which stimulates guanylate cyclase-C in the intestine, to develop a pipeline of soluble guanylate cyclase (sGC) stimulators. sGC plays an important role in regulating diverse physiological processes; dysregulation of sGC may play a role in multiple serious diseases. Ironwood's sGC stimulators are believed to harness the nitric oxide (NO)/sGC/cGMP pathway by working synergistically with NO to improve blood flow and metabolism and decrease inflammation and fibrosis.

Ironwood is advancing praliciguat (IW-1973) for the potential treatment of diabetic nephropathy and of heart failure with preserved ejection fraction (HFpEF). Olinciguat (IW-1701) is being developed for the potential treatment of achalasia and of sickle cell disease. In addition, Ironwood has a pipeline of other sGC stimulators in pre-clinical development.

About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is a commercial biotechnology company focused on creating medicines that make a difference for patients, building value for our fellow shareholders, and empowering our passionate team. We are commercializing two innovative primary care products: linaclotide, the U.S. branded prescription market leader for adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), and lesinurad, which is approved to be taken with a xanthine oxidase inhibitor (XOI), or as a fixed-dose combination with allopurinol, for the treatment of hyperuricemia associated with gout. We are also advancing a pipeline of innovative product candidates in areas of significant unmet need, including persistent gastroesophageal reflux disease, diabetic nephropathy, heart failure with preserved ejection fraction, achalasia and sickle cell disease. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. For more information, please visit www.ironwoodpharma.com or www.twitter.com/ironwoodpharma; information that may be important to investors will be routinely posted in both these locations.

Forward-Looking Statements

This press release contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements about Ironwood's sGC program and the clinical program for praliciguat; the assessment of the data from the clinical trials of praliciguat; the mechanism of action of praliciguat; prevalence and unmet need; the development, regulatory and commercialization plans for praliciguat; and praliciguat as a potential treatment for diabetic nephropathy and HFpEF. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to preclinical and clinical development, manufacturing and formulation development; the risk that future clinical studies need to be discontinued for any reason, including safety, tolerability, enrollment, manufacturing or economic reasons; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of praliciguat; the risk that the therapeutic opportunities for praliciguat are not as we expect; decisions by regulatory authorities; the risk that we may never get sufficient patent protection for praliciguat or that we are not able to successfully protect such patents; the outcomes in legal proceedings to protect or enforce the patents relating to praliciguat; developments in the intellectual property landscape; challenges from and rights of competitors or potential competitors; the risk that our planned investments do not have the anticipated effect on our business or the praliciguat program; and those risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, and in our subsequent SEC filings. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Ironwood undertakes no obligation to update these forward-looking statements.

¹ "Insulin Sensitivity." Diabetes.co.uk. <https://www.diabetes.co.uk/insulin/insulin-sensitivity.html>. Accessed June 14, 2018.

² Salvetti A, Brogi G, Di Legge V, Bernini GP. (1993). The inter-relationship between insulin resistance and hypertension. *Drugs*. 1993;46 Suppl 2:149-59. <https://www.ncbi.nlm.nih.gov/pubmed/7512468>

³ Walldius, G., & Junger, I. (2004). Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. *Journal of Internal Medicine*, 255(2), 188-205. <https://www.ncbi.nlm.nih.gov/pubmed/14746556>



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