Ironwood Reports Top-line Phase IIa Data for IW-1973 Demonstrating Positive Cardiovascular, Metabolic and Endothelial Effects

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- Addition of IW-1973 to ongoing medical regimens used to treat diabetic patients with hypertension showed reductions in blood pressure, fasting plasma glucose, cholesterol and triglycerides, and improved endothelial function -

-Data support advancement of IW-1973 for evaluation as a potential treatment for patients with diabetic nephropathy and for patients with heart failure with preserved ejection fraction -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ:IRWD) today announced encouraging top-line results from two Phase IIa studies of IW-1973, Ironwood's lead investigational soluble guanylate cyclase (sGC) stimulator, in patients with type 2 diabetes and hypertension. Consistent with pre-clinical observations, in both studies treatment with IW-1973 led to blood pressure reductions and improvements in metabolic parameters, including reductions in fasting plasma glucose and cholesterol levels, in patients who were taking a stable regimen of therapies to manage their disease. Elevated levels of plasma cGMP provided clear evidence of target engagement. These studies confirm a pharmacokinetic profile of IW-1973 supporting once-daily dosing and suggest broad distribution to tissues, offering the potential for extra-vascular pharmacology. IW-1973 was generally well-tolerated.

Ironwood is currently developing IW-1973 for the treatment of diabetic nephropathy and for the treatment of heart failure with preserved ejection fraction (HFpEF). The company recently initiated two new Phase II dose-ranging clinical trials with IW-1973 in these indications.

"We are encouraged by the pharmacokinetic profile of IW-1973 that supports a once-daily dosing regimen, as well as its safety and tolerability profile, as observed in the Phase IIa studies," said Christopher Wright, MD, PhD, senior vice president of global development and chief development officer at Ironwood. "In addition, we are excited to see signals of a positive impact of IW-1973 on vascular and metabolic biology important to diabetes and heart failure, particularly since they were observed on top of existing therapies. These data further reinforce our commitment to developing IW-1973 in patients with diabetic nephropathy and in patients with HFpEF, two diseases of significant unmet need estimated to affect millions of patients around the world, and we are advancing our ongoing larger Phase II trials in these indications."

The two Phase IIa exploratory studies were designed to evaluate the safety and tolerability, pharmacokinetics and pharmacodynamics of IW-1973 in diabetic patients with hypertension on a stable regimen of medicines to manage their disease. The studies were not designed or powered explicitly to assess efficacy, but the data yielded clear and consistent trends indicating a positive effect of IW-1973 on blood pressure, metabolic parameters and endothelial function biomarkers.

The larger of the two exploratory studies (n=26) was a randomized, placebo-controlled, 14-day study. Participating patients were required to remain on their existing treatment regimens. All were taking at least one medication to manage their hypertension and at least one medication to manage their diabetes; a majority were also taking additional medications to manage their cholesterol and serum lipid levels. Approximate mean baseline pre-treatment characteristics of the study participants were mean arterial blood pressure of 92 mmHg, fasting plasma glucose of 150 mg/dL, serum cholesterol of 156 mg/dL and serum triglycerides of 153 mg/dL. 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 were combined. Top-line data were as follows:

- **Decrease in Blood Pressure:** At day 14, patients treated with IW-1973 showed a mean decrease in mean arterial blood pressure of 6.3 mmHg from baseline compared to a decrease of 1.6 mmHg from baseline in patients treated with placebo, as measured by 24-hour ambulatory blood pressure monitoring (ABPM), which was a 4.7% greater reduction in patients treated with IW-1973 compared to placebo-treated patients.
- **Decrease in Fasting Glucose:** At day 15, following completion of the study treatment regimen, patients treated with IW-1973 showed a mean decrease in fasting plasma glucose of 32.5 mg/dL from baseline compared to a decrease of 19.7 mg/dL from baseline in patients treated with placebo, which was a 10% greater reduction in patients treated with IW-1973 compared to placebo-treated patients.
- **Decrease in Cholesterol:** At day 15, patients treated with IW-1973 showed a mean decrease in serum cholesterol of 24.7 mg/dL from baseline compared to an increase of 0.8 mg/dL from baseline in patients treated with placebo, which was a 15.4% greater reduction in patients treated with IW-1973 compared to placebo-treated patients. The reduction was largely attributable to a decrease in low-density lipoprotein (LDL), the component of total cholesterol associated with long-term cardiovascular risk.
- **Decrease in Triglycerides:** At day 15, patients treated with IW-1973 showed a mean decrease in serum triglycerides of 46.2 mg/dL from baseline compared to a decrease of 32.0 mg/dL from baseline in patients treated with placebo, which was a 14.4% greater reduction in patients treated with IW-1973 compared to placebo-treated patients.
- **Reduction in Biomarker of Endothelial Dysfunction:** Levels of asymmetric dimethylarginine (ADMA), a key biomarker for endothelial dysfunction and cardiovascular risk, were reduced from baseline in patients receiving IW-1973 compared to

patients receiving placebo.

The most common adverse events (AE) reported in patients treated with IW-1973 were headache, hypoglycemia and nausea. Only nausea was present in the IW-1973 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 IW-1973. All other AEs were characterized as mild.

The second, smaller trial (n=11) was an open-label, rapid dose escalation study. Results from this study were similar to those in the 14-day, randomized, placebo-controlled trial, including reductions in blood pressure, fasting plasma glucose, cholesterol and triglyceride levels, and ADMA levels. The most common AE reported was headache. All AEs were characterized as mild or moderate.

About IW-1973

IW-1973, Ironwood's lead 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, IW-1973 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 IW-1973, its lead sGC stimulator, for the potential treatment of diabetic nephropathy and the potential treatment of heart failure with preserved ejection fraction (HFpEF). Ironwood's second clinical sGC stimulator, IW-1701, is being developed for the potential treatment of achalasia and sickle cell disease. In addition, Ironwood has a rich pipeline of other promising sGC stimulators in preclinical 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 for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with a medically appropriate daily dose of a xanthine oxidase inhibitor (XOI) alone. We are also advancing a pipeline of innovative product candidates in areas of significant unmet need, including uncontrolled 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.

This press release contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements about the topline assessment of the data from the clinical trials of IW-1973, including a dosing regimen, safety, and tolerability; the development, regulatory and commercialization plans for IW-1973, and the timing thereof, including further investigation and advancement of IW-1973; the design, potential indications for, and possible benefits of IW-1973 and its potential as a treatment for patients; prevalence and unmet need; and market size, growth and opportunity. 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 IW-1973; the risk that the therapeutic opportunities for IW-1973 are not as we expect; decisions by regulatory authorities; those risks related to competition and future business decisions made by us and our competitors or potential competitors; the risk that we may never get sufficient patent protection for IW-1973 or that we are not able to successfully protect such patents; developments in the intellectual property landscape; and the risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, 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.

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