



Ironwood Pharmaceuticals Presents IW-3718 Data Showing Improvements in Heartburn and Regurgitation Symptoms in Patients with Persistent GERD at Digestive Disease Week® 2018

June 5, 2018

– Also Evidence of Efficacy in Persistent GERD Patients with Erosive Esophagitis –

– Additional Data Presented Further Highlight Role of Bile Acid in Persistent GERD –

– Ironwood Expects to Advance IW-3718 into Phase III Trials in 3Q 2018 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 5, 2018-- [Ironwood Pharmaceuticals, Inc.](#) (NASDAQ: IRWD), a commercial biotech company, today presented data from a double-blind, placebo-controlled, dose-ranging Phase IIb trial evaluating IW-3718 in persistent gastroesophageal reflux disease (GERD) during a distinguished abstract plenary oral session at Digestive Disease Week® (DDW) 2018 in Washington, D.C. The data demonstrated that, compared to placebo, IW-3718 1500 mg plus a once a day proton pump inhibitor (PPI) improved symptoms of heartburn severity in the overall population of GERD patients in the trial. Additionally, new data presented suggested a greater improvement in heartburn severity in the subset patient population of persistent GERD patients who also have erosive esophagitis, a severe inflammation and erosion of the esophagus.^{1,2}

These findings build upon previously reported topline positive results from the trial, which demonstrated that IW-3718 1500 mg plus a PPI significantly reduced heartburn severity and showed reductions in frequency of regurgitation – two of the most bothersome and frequent symptoms of GERD³ – compared to a PPI alone. More than 50% of patients treated with IW-3718 1500 mg plus a PPI reported a clinically meaningful reduction in heartburn severity. Following these positive Phase IIb results, Ironwood expects to initiate Phase III trials during the third quarter of 2018.

“These data are encouraging for physicians who continue to see their patients with GERD struggle with frequent and bothersome symptoms despite taking PPIs,” said Michael Vaezi, M.D., Ph.D. Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Director of the Center for Swallowing and Esophageal Disorders at Vanderbilt University Medical Center and an investigator for the study – who presented the data at DDW. “In addition to holding promise for patients with persistent GERD, these results show that IW-3718 also has potential in patients who also have erosive esophagitis despite PPI therapy – a serious condition that can cause severe damage and injury to the esophagus.”

Persistent GERD affects an estimated 10 million Americans who continue to suffer from heartburn and regurgitation despite receiving treatment with PPIs, the current standard of care, to suppress stomach acid. Bile acids, which are produced in the intestine and play an important role in the digestive process, have been implicated in contributing to GERD symptoms.^{4,5} IW-3718 is a novel formulation of colessevelam, a bile acid sequestrant, designed to release in the stomach over an extended period where it is positioned to intercept bile before it reaches the esophagus.

“The data presented at this meeting provide strong validation of our approach of targeting bile acid reflux in addition to suppressing stomach acid with PPIs and reinforce our belief that IW-3718 may bring a new approach to treating these patients for whom available options don't work,” said Mark Currie, Ph.D., senior vice president, chief scientific officer, and president of research and development at Ironwood. “We are excited by the results and are actively working to start Phase III trials shortly.”

Additional Data Presentations

Additional data presented by the company reinforced the critical role of bile acid in persistent GERD, and showed a correlation between satisfaction with symptom control, health-related quality of life and health care resource utilization in patients with GERD.

Role of Bile Acid in GERD

In a poster presentation titled *Presence of bile acids detected in human saliva using a novel sensitive bioanalytical method: a comparative study in patients with persistent or controlled GERD symptoms and healthy subjects* (poster session Su1089), Nisha Perez, Ironwood Pharmaceuticals, Inc., presented findings from an exploratory saliva bile study using samples from Phase IIb trial that showed higher levels of bile acids were observed in the saliva of patients with persistent GERD relative to controlled GERD patients and healthy subjects. These findings reinforce Ironwood's previous clinical research that showed bile acid plays a key role in the ongoing symptoms of persistent GERD. The presence of bile acid in patients' saliva was measured using a high-performance liquid chromatography-mass spectrometry (HPLC/MS/MS) method that simultaneously monitors ten bile acids with a high degree of sensitivity (≥ 1 nM). These data demonstrate that the HPLC/MS/MS method is highly sensitive and can measure very low amounts of bile acids in human saliva. This approach may be an alternative, noninvasive way to assess if a patient is experiencing bile acid reflux and warrants further evaluation.

Presenting results of a preclinical study, Sarah Jacobson, Ironwood Pharmaceuticals, Inc., provided insight on the ex vivo effect of the bile acid sequestrant colessevelam on the contractile activity of the lower esophageal sphincter (LES) muscle, dysfunction of which is believed to be the most common cause of GERD.⁶ In a poster presentation titled *Bile acid sequestrant shows effects on the contractile activity of ex-vivo lower esophageal sphincter muscle* (poster session Mo1515), Jacobson presented data demonstrating that colessevelam attenuated bile acid-induced relaxation of rat and human LES muscle tissue. These findings suggest that IW-3718 sequestration of refluxed bile acid in the intestine/stomach of patients with persistent GERD has potential to prevent bile-induced LES muscle relaxation. This mechanism may have contributed to the results observed in patients in the Phase IIb clinical trial of IW-3718.

Characteristics of GERD Patients with Satisfactory or Unsatisfactory Symptom Control

In a poster presentation titled *Gastroesophageal reflux disease (GERD) patients taking proton pump inhibitors: characteristics of those with satisfactory or unsatisfactory control of their condition* (poster session Sa1097), Colin Howden, M.D., The University of Tennessee Health Science Center, Memphis, TN, presented data from a 2017 cross-sectional survey of U.S. adults confirming that while symptoms are adequately controlled for most patients with GERD who are treated with PPIs, symptoms persist despite PPI treatment for many patients. Among survey respondent GERD patients who were treated with a PPI, those who were dissatisfied with their symptom control reported lower health-related quality of life and greater healthcare resource utilization than those who were satisfied.

About IW-3718

IW-3718 is a novel, gastric retentive formulation of colesevelam, a bile acid sequestrant, developed by Ironwood using the proprietary Acuform® drug delivery formulation technology licensed from Depomed, Inc. IW-3718 is designed to deliver the bile acid sequestrant to the stomach over an extended period of time where it is positioned to intercept bile before it reaches the esophagus. Data from non-clinical and clinical studies collectively support the extended release and gastric-retentive profile of IW-3718. Ironwood has existing patents and pending patent applications for IW-3718 that are expected to provide patent coverage into the mid-2030s.

About Persistent Gastroesophageal Reflux Disease (GERD)

An estimated 10 million adult Americans and more than 60 million adult patients globally suffer from persistent gastroesophageal reflux disease (GERD), meaning they continue to experience symptoms such as heartburn and regurgitation despite receiving treatment with a proton pump inhibitor (PPI). While PPIs suppress production of stomach acid, Ironwood's clinical research demonstrates that reflux of bile from the intestine into the stomach and esophagus plays a key role in the ongoing symptoms of persistent GERD. FDA-approved treatment options for these patients are limited.

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 prevalence of persistent GERD; the anticipated timing of initiation of the persistent GERD Phase III trial; and the expected period of patent coverage for IW-3718. Applicable risks and uncertainties include those related to preclinical and clinical development, manufacturing and formulation development; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of IW-3718; decisions by regulatory and judicial authorities; the risk that we are unable to successfully commercialize IW-3718, if approved; the risk that we may never get sufficient patent protection for IW-3718 or that we are not able to successfully protect such patents; the outcomes in legal proceedings to protect or enforce the patents relating to our products and product candidates; 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 company revenues, products or product candidates; the risk that we are unable to manage our operating expenses or cash use for operations, or are unable to commercialize our products, within the guided ranges or otherwise as expected; and the 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 Lynch, Kristle Lee (2018). Gastroesophageal Reflux Disease (GERD). The Merck manual online. Retrieved from: <https://www.merckmanuals.com/home/digestive-disorders/esophageal-and-swallowing-disorders/gastroesophageal-reflux-disease-gerd>

²National Center for Biotechnology Information. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5. Retrieved from: <https://www.ncbi.nlm.nih.gov/books/NBK47264/>

³ Vakil, N., Stelwag M., Shea E.P., & Miller S. (2015). Symptom Burden and Consulting Behavior in Patients with Overlapping Functional Disorders in the US Population. *United European Gastroenterology Journal*, 4(3), 412-422.

⁴ Bachir G. S., Leigh-Collis J., Wilson P., & Pollak E. W. (1981). Diagnosis of incipient reflux esophagitis: a new test. *Southern Medical Journal*, 74(9), 1072-4.

⁵ Vaezi M. F., & Richter J. E. (1998). Contribution of acid and duodenogastro-oesophageal reflux to oesophageal mucosal injury and symptoms in partial gastrectomy patients. *Gut*, 41, 297-302.

⁶ Mitre, M. C., & Katzka, D. A. (2004). Pathophysiology of GERD: Lower Esophageal Sphincter defects. *Practical Gastroenterology*, 28(5), 44-58.

View source version on businesswire.com: <https://www.businesswire.com/news/home/20180605006518/en/>

Source: Ironwood Pharmaceuticals, Inc.

Ironwood Pharmaceuticals, Inc.
Meredith Kaya, 617-374-5082
Vice President, Investor Relations and Corporate Communications
mkaya@ironwoodpharma.com