Ironwood Pharmaceuticals Initiates Pivotal Phase III Program for IW-3718 in Persistent Gastroesophageal Reflux Disease

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– Program Designed to Support U.S. Regulatory Filing of IW-3718 as Potential Treatment for Patients Who Continue to Suffer From GERD Despite Receiving Standard of Care –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 21, 2018-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD), a commercial biotech company, today announced the initiation of two Phase III clinical trials evaluating the safety and efficacy of IW-3718 in patients with persistent gastroesophageal reflux disease (GERD). Persistent GERD affects an estimated 10 million Americans who continue to suffer from heartburn and regurgitation despite receiving treatment with proton pump inhibitors (PPIs), the current standard of care.

"We are excited to advance development of IW-3718 by initiating the Phase III trials," said Christopher Wright, M.D., Ph.D., senior vice president, global development and chief development officer at Ironwood."Pre-clinical and clinical evidence suggest that IW-3718 may offer a treatment option for the millions of patients with GERD who continue to experience frequent and bothersome symptoms such as heartburn and regurgitation despite taking PPIs. Our teams have done excellent work to rapidly initiate these trials. We are hopeful that these studies will generate data in support of a potential approval as quickly as possible."

The Phase III program comprises two identical randomized, double-blind, placebo-controlled, multicenter Phase III trials that target enrolling approximately 1,320 patients total (660 in each trial) with persistent GERD who demonstrate evidence of pathological acid reflux. Eligible patients will continue to take PPIs and be randomized to placebo or IW-3718 1500 mg twice a day for eight weeks.

The primary endpoint is overall heartburn responder, defined as a patient who experiences at least a 45% reduction from baseline in heartburn severity (an improvement determined to be clinically meaningful based on patient-reported outcomes in the Phase IIb trial) for at least four out of eight weeks, including at least one of the last two weeks. Secondary endpoints include change in weekly heartburn severity, change in weekly regurgitation frequency and the proportion of heartburn-free days.

Data from the 280 patient IW-3718 Phase IIb trial in patients with persistent GERD showed that 1500 mg twice daily as an adjunct therapy to PPIs significantly reduced heartburn severity and showed reductions in frequency of regurgitation – two of the most bothersome and frequent symptoms of GERD – compared to a PPI alone. The most common adverse event reported overall in the Phase IIb trial was constipation (IW-3718 + PPI = 7.4% vs. PPI alone = 7.1%); all constipation adverse events reported were mild or moderate in severity. Discontinuation rates due to adverse events were less than 5% and similar across treatment groups.

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 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 proton pump inhibitors (PPIs). 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 ironwoodpharma.com/ or 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, program design, the generation of data in support of a potential approval, 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.

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