July 20, 2017

Ironwood Pharmaceuticals Reports Positive Top-line Results from IW-3718 Phase IIb Trial in Uncontrolled Gastroesophageal Reflux Disease

- IW-3718 1500 mg demonstrated a significant reduction in heartburn severity in patients with uncontrolled GERD -

- Greater than 50% of patients treated with IW-3718 1500 mg achieved a clinically meaningful reduction in heartburn severity -

- IW-3718 1500 mg also showed reductions in regurgitation frequency -

- Ironwood expects to advance IW-3718 into Phase III -

- Conference call scheduled today at 8:30 a.m. ET -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD), a commercial biotechnology company, announced positive top-line data from a Phase IIb clinical trial evaluating IW-3718 in adult patients with uncontrolled gastroesophageal reflux disease (GERD). The trial met its primary endpoint, indicating that twice-daily, oral dosing of IW-3718 1500 mg plus a proton pump inhibitor (PPI) significantly reduced heartburn severity in patients with uncontrolled GERD compared to patients treated with a PPI alone. Further, more than half of patients treated with IW-3718 1500 mg plus a PPI achieved a clinically meaningful reduction in heartburn severity. IW-3718 1500 mg was well tolerated in the trial. Ironwood plans to have end of Phase II meetings with the U.S. Food and Drug Administration (FDA), after which the company expects to advance IW-3718 1500 mg into Phase III development in the second half of 2018.

Uncontrolled GERD is a chronic condition affecting an estimated 10 million Americans who continue to suffer from symptoms such as heartburn and regurgitation despite receiving treatment with PPIs - the current standard of care - to suppress acid produced in the stomach. Ironwood's clinical research has demonstrated that reflux of bile from the intestine into the stomach and esophagus plays a key role in the ongoing symptoms of uncontrolled GERD. IW-3718 is a novel formulation of a bile acid sequestrant designed to release in the stomach over an extended period of time, bind to bile that refluxes into the stomach, and potentially provide symptomatic relief in uncontrolled GERD.

"Millions of patients with GERD globally are significantly impacted by frequent and bothersome heartburn and regurgitation symptoms despite diligently taking their PPIs. They are seeking relief, asking for new treatment options and we really have nothing to offer them," said Michael Vaezi, M.D., Ph.D., professor of medicine, division of gastroenterology and hepatology, director of the Center for Swallowing and Esophageal Disorders at Vanderbilt University Medical Center and an investigator for the study. "The data from this trial are encouraging, as they provide strong evidence that bile plays a key role in uncontrolled GERD and that IW-3718 may bring a much-needed new approach to treating these patients."

Data from the Phase IIb trial showed a dose response across the primary and key secondary endpoints, with the most pronounced response observed at the highest dose of IW-3718 studied (1500 mg). Top-line data were as follows:

- **Percent Change from Baseline to Week 8 in Weekly Heartburn Severity (primary endpoint):** patients treated with IW-3718 1500 mg plus a PPI showed a mean decrease of 58.0% from baseline in heartburn severity compared to 46.0% in patients treated with a PPI alone ($p = 0.04$).
- **Clinically Meaningful Degree of Improvement in Weekly Heartburn Severity:** a 45% reduction in weekly heartburn severity was determined to be clinically meaningful for patients in this study based on patient-reported outcome measures.
- **Heartburn Responder:** a heartburn responder was defined as a patient who experienced at least a 45% reduction from baseline in heartburn severity for at least four out of eight weeks, including at least one of the last two weeks. 52.9% of patients treated with IW-3718 1500 mg plus a PPI were heartburn responders, compared to 37.1% of patients treated with a PPI alone.
- **Percent Change from Baseline to Week 8 in Weekly Regurgitation Frequency:** patients treated with IW-3718 1500 mg plus a PPI showed a mean decrease of 55.4% from baseline in regurgitation frequency compared to 37.9%

in patients treated with a PPI alone (among patients with baseline regurgitation; p = 0.01).

There were no treatment-related serious adverse events reported with IW-3718 1500 mg. The most common adverse event reported overall was constipation, which was reported in 7.4% of patients on IW-3718 1500 mg plus a PPI (n=5) compared to 7.1% of patients on a PPI alone (n=5). 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.

"The results from this trial, demonstrating encouraging improvements in heartburn severity and regurgitation, appear to validate our approach of targeting bile acid reflux in patients with uncontrolled GERD in addition to suppressing acid with PPIs," said Mark Currie, Ph.D., senior vice president, chief scientific officer, and president of research and development at Ironwood. "These data were consistent and robust across key endpoints, and reinforce our belief that IW-3718 may lead to meaningful symptom relief for patients with uncontrolled GERD."

Ironwood intends to present additional data from the Phase IIb clinical trial at an upcoming scientific meeting and/or via peer-reviewed publications.

IW-3718 is wholly-owned by Ironwood. Ironwood has existing patents and pending patent applications for IW-3718 that are expected to provide patent coverage into the mid-2030s.

Conference Call Information

Ironwood will host a conference call and webcast at 8:30 a.m. Eastern Time on Thursday, July 20, 2017, to discuss the top-line results of the IW-3718 Phase IIb clinical trial. Individuals interested in participating in the call should dial (877) 643-7155 (U.S. and Canada) or (914) 495-8552 (international) using conference ID number 58702323. To access the webcast, please visit the Investors section of Ironwood's website at www.ironwoodpharma.com at least 15 minutes prior to the start of the call to ensure adequate time for any software downloads that may be required. The call will be available for replay via telephone starting at approximately 11:30 a.m. Eastern Time, on July 20, 2017 running through 11:59 p.m. Eastern Time on July 27, 2017. To listen to the replay, dial (855) 859-2056 (U.S. and Canada) or (404) 537-3406 (international) using conference ID number 58702323. The archived webcast will be available on Ironwood's website for 14 days beginning approximately one hour after the call has completed.

Phase IIb Trial Design

The randomized, double-blind, placebo-controlled Phase IIb clinical trial enrolled 282 adult patients with GERD (including 276 adult patients with baseline regurgitation), confirmed by endoscopy, who were taking a PPI and continuing to experience GERD symptoms, including heartburn and regurgitation, at least four days per week during the previous eight weeks. The trial included a two-week pretreatment period, during which baseline symptoms were assessed via an electronic diary. Patients were then randomly assigned to receive either placebo or one of three doses of IW-3718 (500 mg, 1,000 mg or 1,500 mg) twice daily for eight weeks, in addition to their daily PPI therapy. The primary efficacy endpoint was percent change in weekly heartburn severity from baseline to week 8. Additionally, a heartburn responder endpoint was defined based on a clinically meaningful degree of improvement derived for the uncontrolled GERD population from patient reported outcome measures collected in the study. No adjustments were made for multiplicity; p-values were reported as nominal.

About IW-3718

IW-3718 is a novel, gastric retentive formulation of 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 Uncontrolled Gastroesophageal Reflux Disease (GERD)

An estimated 10 million adult Americans and more than 60 million adult patients globally suffer from uncontrolled 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 uncontrolled 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) for the treatment of hyperuricemia associated with uncontrolled gout. We are also advancing a pipeline of internally and externally generated innovative product candidates in areas of significant unmet need, including uncontrolled gastroesophageal reflux disease and vascular and fibrotic diseases. 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.

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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 Phase IIb clinical trial of IW-3718; the development, regulatory and commercialization plans for IW-3718, and the timing thereof, including further investigation and advancement of IW-3718, engaging with the FDA, advancing IW-3718 into Phase III development and commercializing IW-3718 within and outside the U.S.; the design of the Phase IIb trial and its impact on the results thereof, as well as the results and their validation of our approach to targeting bile acid reflux in patients with uncontrolled GERD and expectations relating to replication in Phase III; the timing of presentation of additional IW-3718 Phase IIb data; the design, potential indications for, and possible benefits of IW-3718 and its potential as a treatment for patients with uncontrolled GERD; the potential for patient adherence to IW-3718; the level of competition in the uncontrolled GERD space; physicians' willingness to adopt and the potential for broad payer access and reimbursement; prevalence and unmet need; market size, growth and opportunity, including peak sales and potential demand for IW-3718 in the U.S.; and the strength of the intellectual property protection for IW-3718. 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-3718; the risk that the therapeutic opportunities for IW-3718 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-3718 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 March 31, 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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