Ironwood Pharmaceuticals Initiates Phase IIIb Study of Linaclotide in Adult Patients with Irritable Bowel Syndrome with Constipation (IBS-C)

July 16, 2018

– Trial designed to more comprehensively evaluate the effect of linaclotide 290 mcg on bothersome abdominal symptoms, including bloating, discomfort and pain, associated with IBS-C –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 16, 2018-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD), a commercial biotech company, today announced the initiation of a Phase IIIb clinical trial evaluating the efficacy and safety of linaclotide 290 mcg on multiple abdominal symptoms in addition to pain, including bloating and discomfort, in adult patients with irritable bowel syndrome with constipation (IBS-C). Linaclotide is a guanylate cyclase-C (GC-C) agonist approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with IBS-C or chronic idiopathic constipation (CIC).

“There are an estimated 13 million adult IBS-C patients in the U.S., and more than two thirds of them report suffering from symptoms such as abdominal bloating and discomfort at least once per week. These symptoms are often a primary complaint and reason for patients seeking care,” said Christopher Wright, M.D., Ph.D., senior vice president, global development and chief development officer at Ironwood. “As IBS-C patients often describe their abdominal symptoms as bloating or discomfort, rather than pain, this can lead to under-treatment. If positive, we believe these data should further enable more effective communication between patients and physicians on both IBS-C and the role that linaclotide can play in treating the millions of appropriate patients suffering from IBS-C.”

The randomized, double-blind, placebo-controlled, parallel-group study aims to enroll approximately 600 adult IBS-C patients in the United States. Eligible patients will be randomized to placebo or linaclotide 290 mcg once daily for 12 weeks, followed by a four-week randomized withdrawal period.

The primary efficacy endpoint is change from baseline in abdominal score based on daily patient assessments of abdominal bloating, discomfort, and pain at their worst, as reported on an 11-point numerical rating scale. Additional endpoints include change from baseline in spontaneous bowel movement (SBM) frequency, complete spontaneous bowel movement (CSBM) frequency, stool consistency, and straining.

The clinical trial is being conducted jointly by Ironwood and Allergan plc, Ironwood's co-development and co-promotion partner for linaclotide in the United States.

About Linaclotide

Linaclotide is a guanylate cyclase-C (GC-C) agonist that binds to the GC-C receptor locally, within the intestinal epithelium. Linaclotide is marketed by Ironwood and Allergan plc in the United States as LINZESS® and is indicated for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), with greater than 2 million unique patients in the United States having filled approximately 10.6 million linaclotide prescriptions since launch, according to IQVIA. In Europe, Allergan markets linaclotide under the brand name CONSTELLA® for the treatment of adults with moderate to severe IBS-C. In Japan, Ironwood's partner Astellas markets linaclotide under the brand name LINZESS for the treatment of adults with IBS-C. Ironwood also has partnered with AstraZeneca for development and commercialization of linaclotide in China, Hong Kong and Macau, and with Allergan for development and commercialization of linaclotide in all other territories worldwide.

Important Safety Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

LINZESS is contraindicated in patients less than 6 years of age. In nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration. Use of LINZESS should be avoided in patients 6 years to less than 18 years of age. The safety and effectiveness of LINZESS has not been established in patients less than 18 years of age.

Contraindications

LINZESS is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.

LINZESS is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions

Pediatric Risk

LINZESS is contraindicated in patients less than 6 years of age. The safety and effectiveness of LINZESS in patients less than 18 years of age have not been established. In neonatal mice, linaclotide increased fluid secretion as a consequence of GC-C agonism resulting in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of

age and older to develop severe diarrhea and its potentially serious consequences.

Use of LINZESS should be avoided in pediatric patients 6 to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, use of LINZESS should be avoided in pediatric patients 6 years to less than 18 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in LINZESS treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. The incidence of diarrhea was similar in the IBS-C and CIC populations. Severe diarrhea was reported in 2% of 145 mcg and 290 mcg LINZESS treated patients, and in < 1% of 72 mcg LINZESS treated CIC patients. If severe diarrhea occurs, dosing should be suspended and the patient rehydrated.

Common Adverse Reactions (incidence ≥2% and greater than placebo)

In IBS-C clinical trials: diarrhea (20% vs 3% placebo), abdominal pain (7% vs 5%), flatulence (4% vs 2%), headache (4% vs 3%), viral gastroenteritis (3% vs 1%) and abdominal distension (2% vs 1%).

In CIC trials of a 145 mcg dose: diarrhea (16% vs 5% placebo), abdominal pain (7% vs 6%), flatulence (6% vs 5%), upper respiratory tract infection (5% vs 4%), sinusitis (3% vs 2%) and abdominal distension (3% vs 2%). In a CIC clinical trial of a 72 mcg dose: diarrhea (19% vs 7% placebo) and abdominal distension (2% vs < 1%).

Please see full Prescribing Information: http://www.allergan.com/assets/pdf/linzess_pi

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, but not limited to, statements about the size and scope of the Phase IIIb study of linaclotide in adults with IBS-C; the design of the Phase IIIb study, the number of patients expected to be enrolled, endpoints and the data to be generated, including the impact on IBS-C symptoms; the potential for linaclotide to offer IBS-C patients relief from bothersome symptoms including abdominal bloating, abdominal discomfort, and abdominal pain; and IBS-C symptoms and the size of the potential patient population. 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 findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of linaclotide; decisions by regulatory and judicial authorities; the risk that we are unable to successfully commercialize linaclotide; the risk that we may never get sufficient patent protection for linaclotide 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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