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Ironwood Reports Positive Top-Line Results from Phase III Trial of 72 mcg Linaclotide in Adults with Chronic Idiopathic Constipation

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) announced today that the Phase III clinical trial of its 72 mcg dose of linaclotide in adults with chronic idiopathic constipation (CIC) met the primary endpoint. Ironwood and partner Allergan plc intend to submit a supplemental new drug application to the U.S. Food and Drug Administration (FDA) in the first half of 2016.

Linaclotide is currently approved by the FDA as a 145 mcg capsule to be taken once per day for the treatment of adults with CIC and as a 290 mcg capsule to be taken once per day for the treatment of adults with irritable bowel syndrome with constipation (IBS-C).

Top-line data from the Phase III trial indicate that the 72 mcg dose of linaclotide demonstrated statistically significant improvement compared to placebo on the 12-week Complete Spontaneous Bowel Movements (CSBM) Overall Responder endpoint, the primary endpoint for the trial. Additionally, in a pre-specified sensitivity analysis, the 72 mcg dose of linaclotide demonstrated statistically significant improvement compared to placebo on the Durable CSBM Overall Responder endpoint, which is currently being requested by the FDA for Phase III CIC trials. Both the 72 mcg and 145 mcg linaclotide doses were generally well-tolerated in this trial. Consistent with previous Phase III trials of linaclotide, the most common adverse event reported in linaclotide-treated patients was diarrhea. The majority of diarrhea cases reported were characterized as mild in severity. The rates of diarrhea and of discontinuations due to diarrhea were lower for the 72 mcg dose than the 145 mcg dose in this trial.

"Linaclotide is the branded prescription market leader in the treatment of IBS-C and CIC, and we believe the availability of a 72 mcg dose could enhance its utility to physicians for use across the broad, heterogeneous CIC patient population, which encompasses some 35 million adult Americans," said Tom McCourt, chief commercial officer at Ironwood. "With the successful completion of this trial, linaclotide has met all primary endpoints in all seven of its Phase III trials - spanning three doses and two indications. We are committed to continuing to innovate with this molecule, and we are developing multiple additional indications and formulations that, if approved, can address a broad spectrum of patient needs."

The randomized, double-blind, placebo-controlled, multi-site Phase III clinical trial enrolled 1,223 adult patients with CIC. Patients with CIC were defined as having fewer than three spontaneous bowel movements per week, and they also may have experienced recurrent straining, lumpy or hard stools, and/or a sensation that they have not had a complete bowel movement. Patients were randomized to receive 72 mcg of linaclotide once per day, 145 mcg of linaclotide once per day, or placebo once per day for 12 weeks. A 12-week CSBM Overall Responder was defined as a patient who experienced at least three CSBMs per week and an increase of at least one CSBM from baseline in the same week (Weekly Responder), and achieved both of these measures for nine out of 12 weeks. A Durable 12-week CSBM Overall Responder comprises patients that were 12-week CSBM Overall Responders and also met the Weekly Responder criteria for at least three of the last four weeks. The 145 mcg dose was included as a positive control and supported the validity of the trial for evaluation of the 72 mcg dose.

About Chronic Idiopathic Constipation

Chronic idiopathic constipation (CIC) is a functional gastrointestinal disorder in which individuals have infrequent bowel movements (less than three times per week) and also may experience recurrent straining, lumpy or hard stools, and/or a sensation that their bowels are not fully empty. While estimates vary, as many as 35 million adult Americans may suffer from CIC. Results derived from responses to a web-based survey commissioned by Forest Pharmaceuticals, now a member of the Actavis Group plc, and Ironwood suggest that only 12 percent of adult CIC sufferers are medically diagnosed. There are few available prescription treatment options for this condition.

About Linaclotide

Linaclotide is a guanylate cyclase‑C (GC‑C) agonist that is thought to work in two ways based on nonclinical studies. Linaclotide binds to the GC-C receptor locally, within the intestinal epithelium. Activation of GC-C results in increased intestinal fluid secretion and accelerated transit and a decrease in the activity of pain-sensing nerves in the intestine. The clinical relevance of the effect on pain fibers, which is based on nonclinical studies, has not been established. Linaclotide is marketed by Ironwood and Actavis 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). Linaclotide is marketed by Almirall, S.A. for the treatment of adults with moderate to severe IBS-C in Europe under the brand name CONSTELLA®. Ironwood also has partnered with Astellas Pharma Inc. for development and commercialization of linaclotide in Japan and with AstraZeneca for development and commercialization in China.

Important Safety Information

WARNING: PEDIATRIC RISK

LINZESS is contraindicated in pediatric patients under 6 years of age. In nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration in young juvenile mice. Use of LINZESS should be avoided in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age.

Contraindications

- LINZESS is contraindicated in pediatric patients under 6 years of age.
- LINZESS is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions

Pediatric Risk

- LINZESS is contraindicated in children under 6 years of age. The safety and effectiveness of LINZESS in pediatric patients under 18 years of age have not been established. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop significant diarrhea and its potentially serious consequences.
- Use of LINZESS should be avoided in pediatric patients 6 through 17 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 through 17 years of age.

Diarrhea

- Diarrhea was the most common adverse reaction of LINZESS-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. Severe diarrhea was reported in 2% of LINZESS-treated patients. The incidence of diarrhea was similar in the IBS-C and CIC populations.
- Patients should be instructed to stop LINZESS if severe diarrhea occurs and to contact their healthcare provider. The healthcare provider should consider dose suspension and rehydration.

Adverse Reactions

- In IBS-C clinical trials, the most common adverse reactions in LINZESS-treated patients (incidence ≥2% and greater than placebo) were 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 clinical trials, the most common adverse reactions in LINZESS-treated patients (incidence ≥2% and greater than placebo) were 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%).

Please see full Prescribing Information including Boxed Warning: http://www.frx.com/pi/linzess_pi.pdf

About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is focused on creating medicines that make a difference for patients, building value to earn the continued support of our fellow shareholders, and empowering our team to passionately pursue excellence. We discovered, developed and are commercializing linaclotide, which is approved in the United States and a number of other countries. Our pipeline priorities include exploring further opportunities for linaclotide, as well as leveraging our therapeutic expertise in gastrointestinal disorders and our pharmacologic expertise in guanylate cyclases to address patient needs across

the upper and lower gastrointestinal tract. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. Connect with us at www.ironwoodpharma.com or on Twitter at 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, but not limited to, statements about the results of the 72 mcg linaclotide clinical program in CIC; the study's impact on our future plans; the potential for 72 mcg linaclotide to provide physicians with more treatment options and the benefits it may afford adult CIC patients; the ability of our pipeline of guanylate cyclase-C (GC-C) agonists to help patients with gastrointestinal dysfunction, and our exploration thereof; and CIC symptoms, available treatments, the rate of diagnosis 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, but are not limited to, the risks related to decisions related to marketing authorization made by regulatory authorities; the risk that the full data set from such clinical study is not available when we currently anticipate it, is not consistent with this topline data or does not adequately support marketing authorization approval of 72 mcg linaclotide; the risk that the patient population is not as large as we presently estimate; the risks related to the development of our pipeline of GC-C agonists, including efficacy, safety and tolerability; and those risks related to competition and future business decisions made by Ironwood and its competitors or potential competitors. Applicable risks also include those that are listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015, in addition to the risk factors that are listed from time to time in Ironwood's Annual Reports on Form 10‐K, Quarterly Reports on Form 10‐Q and any other subsequent SEC filings. Ironwood undertakes no obligation to update these forward-looking statements to reflect events or circumstances occurring after this press release. Except as otherwise noted, these forward-looking statements speak only as of the date of this press release. All forward‐looking statements are qualified in their entirety by this cautionary statement.

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