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Ironwood Pharmaceuticals Initiates Phase III Trial of 72 mcg Linaclotide in Adult Patients with Chronic Idiopathic Constipation

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) announced today the initiation of a Phase III clinical trial in the U.S. evaluating a 72 mcg capsule of linaclotide to be taken once per day for the treatment of adults suffering from chronic idiopathic constipation (CIC). Linaclotide is currently approved by the U.S. Food and Drug Administration 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).

"The 72 mcg dose of linaclotide may provide physicians with more options that may enable them to better serve their adult chronic idiopathic constipation patients," said Dr. Michael Hall, senior vice president, clinical development of Ironwood. "The development of this additional dosage strength for linaclotide is part of our broader strategy to explore the ability of our pipeline of guanylate cyclase-C agonists to help millions of patients suffering from gastrointestinal dysfunction."

Data from the Phase III trial of 72 mcg linaclotide are expected in 2016. The clinical trial is being conducted jointly by Ironwood and Actavis plc, Ironwood's co-development and co-promotion partner for linaclotide in the United States.

The randomized, double-blind, placebo-controlled, multi-site Phase III clinical trial is expected to enroll approximately 1,200 adult patients with CIC. Patients with CIC have fewer than three spontaneous bowel movements per week, and they also may experience recurrent straining, lumpy or hard stools, and/or a sensation that their bowels are not fully empty. Patients will be randomized to receive 145 mcg of linaclotide once per day, 72 mcg of linaclotide once per day, or placebo once per day for 12 weeks. The primary objective of the trial is to determine the efficacy and safety of linaclotide 72 mcg in adult patients with CIC. The primary efficacy assessment is the percentage of patients who experience at least three complete spontaneous bowel movements (CSBMs) per week and an increase of at least one CSBM from baseline in the same week, and achieve both of these measures for nine out of 12 weeks (12-week CSBM Overall Responder).

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.

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.

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.

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 72 mcg linaclotide clinical program in CIC; the design of the Phase III study, the number of patients expected to be enrolled, endpoints and the data to be generated, including the impact on CIC symptoms; the completion of the Phase III clinical study and the date on which the data from the study is expected to be available; 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 risk that we are unable to enroll as many patients in the clinical study or on the same timeline as we currently anticipate or are otherwise unable to effectively execute on our 72 mcg linaclotide clinical program in CIC; the risk that the clinical study needs to be discontinued for any reason, including safety, efficacy, tolerability, enrollment, manufacturing or economic reasons; those related to decisions made by regulatory authorities; the risk that the data from such clinical study is not available when we currently anticipate it or does not demonstrate efficacy; 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, 2014, 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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