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Ironwood and Allergan Initiate Phase IIb Clinical Trial of Linaclotide Colonic Release in Adults with Irritable Bowel Syndrome with Constipation

CAMBRIDGE, Mass. & DUBLIN--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) and Allergan plc (NYSE: AGN) announced today the initiation of a Phase IIb clinical trial evaluating two orally-administered colonic release formulations of linaclotide in adult patients with irritable bowel syndrome with constipation (IBS-C). The two formulations are being evaluated together in this trial to support potential advancement of two distinct product opportunities into late stage development, one for patients with IBS-C who suffer from both abdominal pain and constipation symptoms, and the other for patients suffering from other gastrointestinal (GI) disorders with lower abdominal pain as a predominant symptom. Data from the Phase IIb clinical trial in IBS-C are expected in the second half of 2016.

Linaclotide is the first and only FDA-approved guanylate cyclase‑C (GC‑C) agonist; it is approved as a 145 mcg capsule to be taken once per day for the treatment of adults with chronic idiopathic constipation (CIC) and as a 290 mcg capsule to be taken once per day for the treatment of adults with IBS-C. Linaclotide binds to the GC-C receptor in the intestine and is thought to work in two ways, based on non-clinical studies: by decreasing the activity of pain-sensing nerves and by increasing fluid secretion into the intestine. The investigational linaclotide colonic release formulations are designed to provide targeted delivery of linaclotide to the distal small intestine and colon, and the companies believe this may further decrease the activity of key pain-sensing nerves in the colon with a smaller increase in fluid secretion.

"Abdominal pain is a key symptom of many gastrointestinal diseases, including IBS-C. Millions of patients are impacted by abdominal pain, and they have few prescription options," said David Nicholson, Ph.D., executive vice president of brand research and development at Allergan. "Our goal in this trial is to evaluate the potential of our two linaclotide colonic release formulations to provide enhanced abdominal pain relief to patients suffering from IBS-C as well as to evaluate the differences between the two formulations and inform a path forward for developing a drug that can reduce gastrointestinal pain in other disorders, such as other types of IBS, ulcerative colitis and diverticulitis."

"With colonic release, we are seeking to peel apart the two components of the linaclotide mechanism of action, which we believe may lead to two product opportunities potentially addressing multiple unmet gastrointestinal needs," said Mark Currie, Ph.D., chief scientific officer and president of research and development at Ironwood. "The colonic release program is one of many efforts by Allergan and Ironwood to tap into linaclotide's rich and pioneering pharmacology as we work together to address the broad spectrum of GI patients' symptoms."

The randomized, double-blind, placebo-controlled, multi-site Phase IIb clinical trial is expected to enroll up to 520 adult patients with IBS-C. Patients will be randomized to one of eight groups: one group receives placebo, one group receives 290 mcg linaclotide (approved formulation), three groups receive various doses of CR1 (colonic release formulation 1 at 30 mcg, 100 mcg or 300 mcg), and three groups receive various doses of CR2 (colonic release formulation 2 at 30 mcg, 100 mcg or 300 mcg). The 290 mcg approved formulation is included as a positive control for this study. All doses will be administered orally, once daily for 12 weeks. The trial is designed to assess the safety and efficacy of each linaclotide colonic release dose and formulation, including its effect on abdominal pain relief and complete spontaneous bowel movement (CSBM) frequency, as well as on other abdominal and bowel symptoms commonly experienced by IBS-C patients. The trial also aims to evaluate how the two colonic release formulations compare to each other and to the approved 290 mcg formulation of linaclotide, with the goal of identifying appropriate doses and formulations for Phase III clinical trials.

About Irritable Bowel Syndrome with Constipation

Irritable bowel syndrome with constipation (IBS-C) is a functional gastrointestinal disorder in which individuals experience hallmark symptoms of abdominal pain and infrequent bowel movements (less than three times per week). While estimates vary, as many as 13 million adults in the U.S. may suffer from IBS-C. Results derived from responses to a web based survey commissioned by Forest Pharmaceuticals and Ironwood Pharmaceuticals suggest that only about half of adult IBS-C 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 Allergan 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 Allergan 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 Allergan

Allergan plc (NYSE: AGN), headquartered in Dublin, Ireland, is a unique, global pharmaceutical company and a leader in a new industry model - Growth Pharma. Allergan is focused on developing, manufacturing and commercializing innovative branded

pharmaceuticals, high-quality generic and over-the-counter medicines and biologic products for patients around the world.

Allergan markets a portfolio of best-in-class products that provide valuable treatments for the central nervous system, eye care, medical aesthetics, gastroenterology, women's health, urology, cardiovascular and anti-infective therapeutic categories, and operates the world's third-largest global generics business, providing patients around the globe with increased access to affordable, high-quality medicines. Allergan is an industry leader in research and development, with one of the broadest development pipelines in the pharmaceutical industry and a leading position in the submission of generic product applications globally.

With commercial operations in approximately 100 countries, Allergan is committed to working with physicians, healthcare providers and patients to deliver innovative and meaningful treatments that help people around the world live longer, healthier lives.

For more information, visit Allergan's website at www.allergan.com.

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.

Statements contained in this press release that refer to future events or other non-historical facts are forward-looking statements that reflect the current perspective of Allergan or Ironwood on existing trends and information as of the date of this release. Except as expressly required by law, Allergan and Ironwood disclaim any intent or obligation to update these forward-looking statements. Actual results may differ materially from the current expectations of Allergan or Ironwood depending upon a number of factors affecting the business of each company. These factors include, among others, the risk that we are unable to complete the Phase IIb clinical study for linaclotide colonic release on the same timeline as we currently anticipate or are otherwise unable to effectively execute on our clinical program for linaclotide colonic release; the risk that the data from such clinical study are not available when we currently anticipate them or do not demonstrate the results we expect, including with respect to efficacy, safety or difference between the two formulations; the risk that the clinical study needs to be discontinued for any reason, including safety, tolerability, enrollment, manufacturing or economic reasons; those related to decisions made by regulatory authorities; those risks related to competition and future business decisions made by us and our competitors or potential competitors; and other risks and uncertainties detailed in the periodic public filings with the Securities and Exchange Commission by both Allergan and Ironwood, including but not limited to each company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 (for Allergan, such periodic public filings having been filed under the "Allergan plc" or "Actavis plc" names) and from time to time in each company's other investor communications. Except as expressly required by law, Allergan and Ironwood disclaim any intent or obligation to update these forward-looking statements.

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