



## **Ironwood Pharmaceuticals Presents Data Further Elucidating Linaclotide's Effect on Pain at Digestive Disease Week® 2017**

- *Linaclotide delayed release improved abdominal pain, independent of effects on bowel function, in a Phase IIb study of patients with IBS-C -*
- *Results from linaclotide preclinical studies suggest potential for effects on visceral hypersensitivity in other conditions associated with visceral pain -*

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- [Ironwood Pharmaceuticals, Inc.](#) (NASDAQ: IRWD), a commercial biotechnology company, this week presented clinical data on the effect of linaclotide on abdominal pain in irritable bowel syndrome with constipation (IBS-C) patients and preclinical data on linaclotide's effect on pain originating in other visceral organs at Digestive Disease Week® (DDW) 2017 in Chicago.

Detailed data from a Phase IIb clinical trial evaluating the effects of two investigational delayed release formulations of linaclotide on abdominal pain in adult patients with IBS-C were presented as a late-breaker by Dr. William Chey, University of Michigan. Ironwood previously reported positive topline data for both delayed release formulations in December 2016. In addition, Ironwood and its collaborators delivered oral and poster presentations at DDW regarding a series of preclinical studies suggesting that linaclotide may have effects on pain associated with conditions affecting visceral organs outside of the gastrointestinal tract, such as the bladder or vagina.

"Millions of patients are estimated to suffer from chronic conditions characterized by pain in the abdominal and pelvic regions, and pain is a primary symptom driving patients to seek treatment from a healthcare provider," said Mark Currie, Ph.D., chief scientific officer and president of research and development at Ironwood. "As we continue to better understand linaclotide's effect on visceral hypersensitivity, we look forward to further studying its ability to relieve pain in IBS-C, as well as potentially in other conditions such as IBS with diarrhea, IBS-Mixed, ulcerative colitis, diverticulitis, interstitial cystitis/bladder pain syndrome and endometriosis."

### **Effect of Linaclotide Delayed Release on Abdominal Pain in IBS-C**

In the Late-Breaking Clinical Science session at DDW, Dr. Chey presented data (poster presentation Tu2031) from a double-blind, placebo-controlled, dose-ranging Phase IIb trial evaluating two investigational delayed release formulations of linaclotide in adult patients with IBS-C.

Data from the Phase IIb study of linaclotide delayed release-1 (DR1) demonstrated dose-dependent improvements in abdominal pain as well as in complete spontaneous bowel movements and stool consistency, compared to placebo, across all studied doses. Additionally, improvements in abdominal pain and stool consistency were greater for the DR1 300 mcg dose compared to the 290 mcg immediate release (IR) formulation of linaclotide. Data from the Phase IIb study of linaclotide delayed release-2 (DR2) showed that all studied doses improved abdominal pain and other abdominal symptoms, relative to placebo, with no apparent effect on bowel movement function, as intended. These comparisons reflect numerical differences. Diarrhea was the most common adverse event. Across all DR1 and DR2 dose groups, 0-3% of patients withdrew from the trial due to diarrhea.

"The data from the linaclotide delayed release study represent a significant advance in the GI field and in our understanding of abdominal pain," said Dr. Chey. "The DR1 data suggest that delaying delivery of linaclotide to the mid-ileum region of the distal small intestine and colon could improve abdominal pain relief while preserving constipation relief. The DR2 data are also exciting: delaying linaclotide delivery to the ileocecal junction in the colon could improve abdominal pain relief with little to no effect on fluid secretion, which could represent a potential opportunity to treat patients suffering from lower gastrointestinal conditions characterized by abdominal pain."

Ironwood and its U.S. collaboration partner Allergan intend to engage with the U.S. Food and Drug Administration (FDA) to discuss Phase III development plans, with trials in adults with IBS-C expected to begin in the second half of 2017. The companies are evaluating DR2 in adult patients with non-constipation subtypes of IBS, and plan to discuss next steps with the FDA for advancing DR2 into Phase IIb dose-ranging clinical trials.

## **Effect of Linaclotide on Various Models of Visceral Hypersensitivity (Preclinical Data)**

In preclinical oral and poster presentations, linaclotide's effects on pain and its potential role in visceral organ cross-sensitization and visceral hypersensitivity were further elucidated.

In a poster presentation titled, *Linaclotide attenuates visceral organ crosstalk: importance of guanylate cyclase c (GC-C) activation in reversing colonic hypersensitivity induced by urinary bladder hyperpermeability* (poster presentation Tu1602), Ehsan Mohammadi, University of Oklahoma Health Science Center, presented preclinical data in a model of colonic hypersensitivity induced by bladder injury, which suggested that oral administration of linaclotide significantly reduced this colonic hypersensitivity, as measured by visceromotor responses (abdominal contractions) to colonic distention and pERK expression (spinal nerve activation). These data suggest that GC-C agonism may be able to affect various abdominal and pelvic area organ pain through visceral organ crosstalk, which is enabled by the fact that multiple organs in this region of the body share sensory peripheral and central innervation pathways.

Just as visceral organ cross-sensitization is hypothesized to explain linaclotide's ability to reduce colonic sensitivity caused by bladder injury, a study by Pei Ge, Ironwood Pharmaceuticals, tested the hypothesis that linaclotide could reduce visceral pain in other pelvic conditions. In a poster presentation titled, *Oral administration of the gut-restricted guanylate cyclase-c agonist, linaclotide, reduces endometriosis-induced vaginal hyperalgesia* (poster presentation Mo1541), both acute and chronic oral administration of linaclotide significantly reduced vaginal pain in a preclinical model of endometriosis, measured by visceromotor responses to vaginal distension. GC-C expression was detected in the intestine, but not in endometrial cysts and the vagina, suggesting that the effect of linaclotide on visceral pain in this model involves shared nervous pathways between visceral organs.

An oral presentation delivered by Stuart Brierley, Ph.D., SAHMRI, Flinders University, Adelaide, SA, Australia, titled *Chronic oral administration of linaclotide inhibits nociceptive signaling in response to noxious colorectal distension in a model of chronic visceral hypersensitivity* (oral presentation 1098) showed the results of a preclinical study evaluating the effects of chronic oral administration of linaclotide on colonic hypersensitivity caused by colorectal distention. In this study, linaclotide reduced colonic hypersensitivity, as measured by visceromotor responses, and also reversed the sprouting of colonic afferent nerves in the spinal cord, which had sprouted in response to pain stimuli in preclinical models. These data suggest that further study is warranted looking into whether linaclotide has the ability to reduce hypersensitivity in the colon and reverse neuroplasticity within the spinal cord associated with chronic visceral hypersensitivity.

Another preclinical study by Dr. Brierley provided additional insight on the mechanism of GC-C agonism in pain reduction by investigating its effects on pain-sensing nerves in the dorsal root ganglia (DRG). In an oral presentation titled, *Extracellular cGMP reduces the excitability of sensory dorsal root ganglion neurons via an extracellular mechanism* (oral presentation 723), he showed that, in this preclinical study, linaclotide did not directly inhibit DRG neurons, but rather its downstream mediator, cyclic guanosine monophosphate (cGMP), was responsible for decreasing activity of these pain-sensing nerves. The study also showed that extracellular cGMP did not enter DRG neurons, lending further support to the hypothesis that cGMP's inhibitory effect is mediated via an extracellular, rather than intracellular, mechanism.

### **About Linaclotide**

Linaclotide is a guanylate cyclase-C (GC-C) agonist that binds to the GC-C receptor locally, within the intestinal epithelium, and is thought to work in two ways, based on nonclinical studies. Activation of GC-C results in increased intestinal fluid secretion and accelerated transit, as well as 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 plc in the United States as LINZESS<sup>®</sup> and is indicated for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), with nearly 1.5 million unique patients in the United States having filled nearly 7.5 million linaclotide prescriptions since launch, according to QuintilesIMS. In Europe, Allergan markets linaclotide under the brand name CONSTELLA<sup>®</sup> 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 and with Allergan for development and commercialization of linaclotide in all other territories worldwide.

### **LINZESS INDICATIONS AND USAGE**

LINZESS (linaclotide) is indicated in adults for the treatment of both irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC).

### **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 have not been established in patients less than 18 years of age.**

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## 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 years 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 $\geq$ 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 trial of a 72 mcg dose: diarrhea (19% vs 7% placebo) and abdominal distension (2% vs < 1%).

Please see full Prescribing Information including Boxed Warning: [http://www.allergan.com/assets/pdf/linzess\\_pi](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) 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](http://www.ironwoodpharma.com) or [www.twitter.com/ironwoodpharma](https://www.twitter.com/ironwoodpharma); information that may be important to investors will be routinely posted in both these locations.

## Forward-Looking Statement

*This press release contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements about the development and commercial potential of linaclotide and the drivers, timing, impact and results thereof; market size, prevalence, and opportunity; the potential indications for, and benefits of, linaclotide; anticipated preclinical, clinical and regulatory activities and developments (including discussions with the FDA) and the design, timing and results of clinical and preclinical studies; and the potential for, and timing of, regulatory submissions and approvals for linaclotide. 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 the effectiveness of development and commercialization efforts by us and our partners; 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 authorities; 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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