



## Ironwood Presents Gastrointestinal Disease Research at Digestive Disease Week® 2015

- Oral and poster presentations feature GC-C agonists linaclotide and IW-9179 -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- [Ironwood Pharmaceuticals, Inc.](#) (NASDAQ: IRWD) announced today that the company and its collaborators will present data from two gastrointestinal disease research programs during Digestive Disease Week® (DDW) 2015 in Washington, D.C., May 16 through May 19, 2015. The presentations include data from multiple studies of linaclotide and IW-9179, both of which are guanylate-cyclase-C agonists, a mechanism of action pioneered by Ironwood scientists.

The data will be presented via oral and poster presentations as follows:

### **Effects of Linaclotide on the GC-C/cGMP Pathway and Related Pain Signaling (Oral Presentation):**

*Chronic Activation of the GC-C/cGMP Pathway by Linaclotide Inhibits Ascending Nociceptive Pathways and Restores Aberrant Spinal Cord Signaling* (presentation # 1028) will be presented during the Sensory Neurobiology Research Forum on Tuesday, May 19, 2015, 2:00 p.m. - 2:15 p.m., by Stuart Brierley, Ph.D., Associate Professor and Head of the Visceral Pain Group, Discipline of Medicine at the University of Adelaide in the Centre for Nutrition and Gastrointestinal Diseases at the South Australian Health and Medical Research Institute (SAHMRI).

### **Effects of GC-C Agonist IW-9179 on Gastric Emptying (Oral Presentation):**

*IW-9179, a Potent Guanylate Cyclase-C (GC-C) Agonist, Improves Gastric Emptying In Vivo and Modulates Gastric Vagal Afferent Mechanosensitivity In Vitro* (presentation # 956) will be presented during the Novel Therapeutic Insights for Motility Disorders Research Forum on Tuesday, May 19, 2015, 10:00 a.m. - 10:15 a.m., by Amanda Page, Ph.D., Associate Professor and Group Leader for the Vagal Afferent Research Group, Discipline of Medicine at the University of Adelaide in the Centre for Nutrition and Gastrointestinal Diseases at the South Australian Health and Medical Research Institute (SAHMRI).

### **Treatment Satisfaction with Linaclotide (Poster Presentation):**

*Effect of Linaclotide on Patient-Reported Confidence in Bowel Movement Success, Predictability of Bowel Movement Timing, and Treatment Satisfaction in Patients with Chronic Idiopathic Constipation and Prominent Abdominal Bloating* (presentation # Sa1397) on Saturday, May 16, 2015, 9:30 a.m. - 4:00 p.m., presented by Douglas Taylor, Director, Health Economics and Outcomes Research at Ironwood Pharmaceuticals, Inc.

### **Understanding the Linaclotide Mechanism of Action (Poster Presentations):**

*Regulation of Linaclotide-Induced cGMP and Electrolyte Secretion by Multidrug Resistance-Associated Protein 4 (MRP4)* (presentation # Mo1886) on Monday, May 18, 2015, 9:30 a.m. - 4:00 p.m., presented by Boris Tchernychev, Ph.D., Senior Scientist at Ironwood Pharmaceuticals, Inc.

*GC-C Agonists as Regulators of Visceral Sensation: Modulation of Mucosal Sensitivity via the Epithelial GC-C/cGMP Pathway* (presentation # Mo1875; Poster of Distinction) on Monday, May 18, 2015, 9:30 a.m. - 4:00 p.m., presented by Joel Castro, Ph.D., Visceral Pain Group, Discipline of Medicine at the University of Adelaide in the Centre for Nutrition and Gastrointestinal Diseases at the South Australian Health and Medical Research Institute (SAHMRI).

*Linaclotide Induces Secretion of cGMP into the Colonic Submucosal Layer: An In Vivo Microdialysis Study in Rats* (presentation # Tu1863) on Tuesday, May 19, 2015, 9:30 a.m. - 4:00 p.m., presented by Jenny Tobin, Senior Associate Scientist at Ironwood Pharmaceuticals, Inc.

### **Potency, Selectivity and Metabolism of GC-C Agonist IW-9179 (Poster Presentation):**

*IW-9179, a Phosphopeptide Designed to Target the Upper Gastrointestinal Tract, is More Potent at Acidic pH, and is Rapidly Metabolized In Vitro in Rodent Intestinal Fluid* (presentation # Tu1211) on Tuesday, May 19, 2015, 9:30 a.m. - 4:00 p.m., by

Marco Kessler, Senior Principal Investigator at Ironwood Pharmaceuticals, Inc.

## 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<sup>®</sup> 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<sup>®</sup>. 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.

LINZESS and CONSTELLA are trademarks owned by Ironwood Pharmaceuticals, Inc. Any other trademarks referred to in this press release are the property of their respective owners. All rights reserved.

## About IBS-C and CIC

While estimates vary, as many as 13 million adults in the U.S. may suffer from IBS-C, and as many as 35 million 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 Pharmaceuticals suggest that only about half of adult IBS-C sufferers are medically diagnosed, and only about 12 percent of adult CIC sufferers are medically diagnosed. Hallmark symptoms associated with IBS-C include abdominal pain and constipation. Symptoms associated with CIC may include constipation, hard or lumpy stools, infrequent stools, and incomplete evacuation (not completely emptying the bowels). There are few available prescription treatment options for these conditions.

## LINZESS Important Safety Information

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### **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.**

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## 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  $\geq 2\%$  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  $\geq 2\%$  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](http://www.frx.com/pi/linzess_pi.pdf).

## About IW-9179

IW-9179 is an investigational GC-C agonist. GC-C is a receptor found mainly on the surface of the intestine and is recognized to be a potential therapeutic target in certain gastrointestinal diseases. Although GC-C is found throughout the gastrointestinal tract, IW-9179 is designed to act primarily in the upper gastrointestinal tract. Ironwood is investigating IW-9179 for the treatment of gastroparesis, with an initial focus on diabetic gastroparesis, and for functional dyspepsia, both of which are upper gastrointestinal disorders characterized by upper abdominal pain, bloating, fullness and nausea, among other symptoms. Data from a Phase I study indicate IW-9179 is minimally absorbed and generally well-tolerated, and initial data from a 10-patient Phase IIa study in which enrollment was limited by stringent inclusion criteria suggest IW-9179 may have applicability in patients with functional dyspepsia. Ironwood is working with gastrointestinal experts and regulatory authorities to define a path forward for IW-9179 in functional dyspepsia. The most common adverse event in both studies was diarrhea.

## About Gastroparesis

Gastroparesis is an upper gastrointestinal disorder in which the muscles and/or nerves of the stomach do not function properly, which disrupts the functional activities of the stomach. Common symptoms of gastroparesis include nausea, vomiting, bloating, upper abdominal pain and feelings of fullness after eating just a few bites of food. Gastroparesis can also result in weight loss and malnutrition. Diabetic gastroparesis, which is the focus of an ongoing Phase IIa study, is a condition in which symptoms of gastroparesis occur in patients with type 1 or type 2 diabetes, and has additional harmful effects on glycemic control, as well as secondary effects on organs, which may lead to increased mortality. Gastroparesis symptoms are reported by approximately five to 12 percent of diabetic patients. There are limited treatment options for gastroparesis available.

## 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](http://www.ironwoodpharma.com) or on Twitter at [www.twitter.com/ironwoodpharma](http://www.twitter.com/ironwoodpharma); information that may be important to investors will be routinely posted in both these locations.

## About Digestive Disease Week (DDW)

Digestive Disease Week<sup>®</sup> (DDW) is the largest international gathering of physicians, researchers and academics in the fields of gastroenterology, hepatology, endoscopy and gastrointestinal surgery. Jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy (ASGE) and the Society for Surgery of the Alimentary Tract (SSAT), DDW takes place May 16-19, 2015, at the Walter E. Washington Convention Center, Washington, DC. The meeting showcases more than 5,000 abstracts and hundreds of lectures on the latest advances in GI research, medicine and technology. More information can be found at [www.ddw.org](http://www.ddw.org).

All data are embargoed until the time of presentation.

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