December 22, 2016

# Ironwood and Allergan Report Topline Phase IIb Data Supporting Advancement of Linaclotide Colonic Release-1 (CR1) in IBS-C

***Abdominal pain improved 56% with CR1 300 mcg relative to placebo in this trial***

***Companies separately announced Phase IIb data with linaclotide colonic release-2 (CR2) supporting investigation in additional GI indications associated with abdominal pain***

***Ironwood to host conference call today at 8:30 a.m. Eastern Time***

CAMBRIDGE, Mass. & DUBLIN--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ:IRWD) and Allergan plc (NYSE:AGN) announced today positive topline data from a Phase IIb clinical trial evaluating the investigational linaclotide colonic release-1 (CR1) formulation in adult patients with irritable bowel syndrome with constipation (IBS-C). Topline data in this trial demonstrated numerically greater abdominal pain improvement with CR1 300 mcg compared to placebo and to the 290 mcg immediate release (IR) formulation of linaclotide. The companies 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.

Linaclotide IR (LINZESS®) is currently FDA-approved and available for the treatment of adults with IBS-C or chronic idiopathic constipation (CIC). Linaclotide 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. Linaclotide CR1 is designed to provide targeted delivery of linaclotide to the distal small intestine and colon, where the majority of the abdominal pain associated with IBS-C is believed to originate. This clinical trial was designed to evaluate whether CR1 could further decrease the activity of key pain-sensing nerves in the distal small intestine and colon while maintaining an effect on fluid secretion. Ironwood and Allergan also announced topline results from the same Phase IIb trial with a second formulation, linaclotide colonic release-2 (CR2), in a separate press release issued today.

"Abdominal pain is usually the most difficult symptom to treat in patients with IBS-C. When that pain is not treated sufficiently, then that drives the patient back into my office again and again," said Philip Schoenfeld, M.D., chief, gastroenterology section, John D. Dingell VA Medical Center and adjunct professor of medicine at the University of Michigan School of Medicine. "I'm encouraged by these initial data. This new formulation of linaclotide may produce additional relief of abdominal pain in patients with IBS-C."

The double-blind, placebo-controlled, dose-ranging Phase IIb trial randomized 532 adult patients with IBS-C into one of eight possible treatment arms. The trial was exploratory in nature and comparisons to placebo were evaluated using nominal p-values. In the trial, CR1 300 mcg demonstrated improvement on the three prespecified key efficacy endpoints as follows:

- **6/12 APC+1 Responder:** the percentage of patients to report at least a 30% reduction from baseline in abdominal pain and an increase of at least one complete spontaneous bowel movement (CSBM) from baseline, both in the same week for at least 6 out of 12 weeks, was 38.8% for CR1 300 mcg compared to 21.2% for placebo and 31.8% for IR 290 mcg.
- **Change from Baseline in Abdominal Pain:** the average weekly change in abdominal pain from baseline to week 12 was -2.14 for CR1 300 mcg compared to -1.37 for placebo and -1.94 for IR 290 mcg, as measured on an 11-point scale. This translates to a 56.2% improvement in abdominal pain with CR1 300 mcg relative to placebo.
- **Change from Baseline in CSBM Frequency:** the average weekly change in CSBM frequency from baseline to week 12 was 1.78 for CR1 300 mcg compared to 1.11 for placebo and 2.11 for IR 290 mcg. This translates to a 59.3% improvement in CSBM frequency with CR1 300 mcg relative to placebo.

In this trial, CR1 300 mcg showed a numerically greater reduction in abdominal pain than IR 290 mcg each week beginning at week 5 and continuing for the remainder of the 12 week study, with a mean percent reduction from baseline at week 12 of 49.5% for CR1 300 mcg compared to 26.2% for placebo and 40.6% for IR 290 mcg. Additionally, patients treated with

linaclotide CR1 300 mcg reported improvement in other abdominal and bowel symptoms commonly experienced by IBS-C patients, including abdominal discomfort and bloating.

The most common adverse event was diarrhea, which was reported in 10.4% of patients on CR1 300 mcg compared to 1.5% of patients on placebo and 13.6% of patients on IR 290 mcg. All diarrhea adverse events reported were mild or moderate in severity, with discontinuation resulting from diarrhea occurring in 3.0% of CR1 300 mcg patients compared to no placebo patients and 6.1% of IR 290 mcg patients.

Additional data from the Phase IIb trial are expected to be shared at upcoming scientific meetings and via peer-reviewed publications.

"Relief of abdominal pain is a key benefit motivating physicians to choose LINZESS for patients suffering from IBS-C, and it is the primary driver of patient satisfaction," said Tom McCourt, chief commercial officer of Ironwood. "We believe the potentially enhanced clinical profile of linaclotide CR1 could support further growth of the LINZESS franchise from $1 billion in U.S. net sales by 2020 to potentially greater than $2 billion in peak U.S. net sales."

"LINZESS is the market-leading U.S. branded prescription medicine for adults with IBS-C or CIC and has been utilized by more than 1 million patients to date," said Bill Meury, chief commercial officer of Allergan. "The CR1 formulation could provide an innovative brand to treat millions of additional suffering patients, extending the success of LINZESS and demonstrating our continued commitment to improving GI care."

Ironwood and Allergan are pursuing patent protection for CR1 and CR2 that, if issued, is expected to provide patent coverage into the mid-2030s.

**Ironwood Conference Call Today at 8:30 a.m. ET:**

Ironwood will host a conference call and webcast at 8:30 a.m. Eastern Time on Thursday, December 22, to discuss the results of the linaclotide colonic release Phase IIb clinical trial. Individuals interested in participating in the call should dial (877) 643-7155 (U.S. and Canada) or (914) 495-8552 (international) using conference ID number 43363931. To access the webcast, please visit the Investors section of Ironwood's website at www.ironwoodpharma.com at least 15 minutes prior to the start of the call to ensure adequate time for any software downloads that may be required. The call will be available for replay via telephone starting at approximately 11:30 a.m. Eastern Time, on December 22, running through 11:59 p.m. Eastern Time on December 29, 2016. To listen to the replay, dial (855) 859-2056 (U.S. and Canada) or (404) 537-3406 (international) using conference ID number 43363931. The archived webcast will be available on Ironwood's website for 14 days beginning approximately one hour after the call has completed.

**Study Design**

Patients in the double-blind, placebo-controlled, dose-ranging Phase IIb clinical trial were randomized to one of eight groups: one group received placebo, one group received linaclotide 290 mcg (approved formulation), three groups received various doses of linaclotide CR1 (30 mcg, 100 mcg or 300 mcg), and three groups received various doses of linaclotide CR2 (30 mcg, 100 mcg or 300 mcg). The 290 mcg approved formulation was included as a reference group for this study. The trial was designed to evaluate the safety and efficacy of each linaclotide colonic release dose and formulation relative to placebo; the statistical power was based on a linear dose response. Additional objectives included assessing how the two colonic release formulations compared to each other and to the approved 290 mcg formulation of linaclotide. All doses were administered orally, once daily for 12 weeks.

**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's partner Astellas received approval of linaclotide in Japan 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.

**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 ≥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.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 advancing a pipeline of innovative medicines in areas of significant unmet need, including irritable bowel syndrome with constipation (IBS-C)/chronic idiopathic constipation (CIC), uncontrolled gout, refractory gastroesophageal reflux disease, and vascular and fibrotic diseases. We discovered, developed and are commercializing linaclotide, the U.S. branded prescription market leader in the IBS-C/CIC category, and we are applying our proven R&D and commercial capabilities to advance multiple internally-developed and externally-accessed product opportunities. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. For more information, please visit www.ironwoodpharma.com or www.twitter.com/ironwoodpharma; information that may be important to investors will be routinely posted in both these locations.

**About Allergan plc**

Allergan plc (NYSE: AGN), headquartered in Dublin, Ireland, is a bold, global pharmaceutical company and a leader in a new industry model - Growth Pharma. Allergan is focused on developing, manufacturing and commercializing branded pharmaceuticals, devices and biologic products for patients around the world.

Allergan markets a portfolio of leading brands and best-in-class products for the central nervous system, eye care, medical aesthetics and dermatology, gastroenterology, women's health, urology and anti-infective therapeutic categories.

Allergan is an industry leader in Open Science, the Company's R&D model, which defines our approach to identifying and developing game-changing ideas and innovation for better patient care. This approach has led to Allergan building one of the broadest development pipelines in the pharmaceutical industry with 65+ mid-to-late stage pipeline programs in development.

Our Company's success is powered by our more than 16,000 global colleagues' commitment to being Bold for Life. Together, we build bridges, power ideas, act fast and drive results for our customers and patients around the world by always doing what is right.

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.

**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 topline assessment of the data from the Phase IIb clinical trial of CR1; the development and regulatory plans for CR1, and the timing thereof, including further investigation and advancement of CR1, engaging with the FDA and advancing CR1 into Phase III; the design of the Phase IIb trial and its impact on the results thereof; the timing of additional Phase IIb data; the potential indications for, and benefits of, CR1; the design and possible benefits of CR1 and its potential as a treatment for patients; prevalence and unmet need; market size, growth and opportunity and potential demand for CR1 in the U.S., including net sales and peak sales; and the strength of the intellectual property protection 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 preclinical and clinical development, manufacturing and formulation development; the risk that future clinical studies need to be discontinued for any reason, including safety, tolerability, enrollment, manufacturing or economic reasons; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of linaclotide; the risk that the therapeutic opportunities for the CR formulations are not as we expect; decisions by regulatory authorities; those risks related to competition and future business decisions made by us and our competitors or potential competitors; the risk that we may never get sufficient patent protection for linaclotide and our product candidates or that we are not able to successfully protect such patents; developments in the intellectual property landscape; and the risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, Allergan's Annual Report on Form 10-K for the year ended December 31, 2015 and in the subsequent SEC filings of each company. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Ironwood and Allergan undertake no obligation to update these forward-looking statements.

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