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## **IRONWOOD AND FOREST ANNOUNCE POSITIVE LINACLOTIDE RESULTS FROM TWO PIVOTAL PHASE 3 TRIALS IN PATIENTS WITH CHRONIC CONSTIPATION**

**—Top-line Results Show Each Trial Met Primary and All Secondary Endpoints —**

*CAMBRIDGE, Mass. and New York, November 2, 2009* — Ironwood Pharmaceuticals, Inc. and Forest Laboratories, Inc. (NYSE: FRX) today announced positive top-line results from two Phase 3 clinical trials assessing the safety and efficacy of once-daily dosing of the investigational drug linaclotide in patients with chronic constipation (CC). Analyses of the data indicate that in both multicenter, randomized, double-blind, placebo-controlled trials, statistical significance was achieved for the primary endpoint of 12-week complete spontaneous bowel movement (CSBM) overall responder at the two doses studied in each trial (133 mcg/day: p-values $\leq$ 0.0012 and 266 mcg/day: p-values $<$ 0.0001). In both trials, statistical significance (p $<$ 0.01) was achieved for all prespecified secondary endpoints, which included measures of bloating, abdominal discomfort, and average weekly CSBMs.

“The results of these two trials confirm the potential for linaclotide to bring relief to the millions of patients suffering from many of the symptoms associated with chronic constipation,” said Howard Solomon, Chairman and Chief Executive Officer of Forest Laboratories. “These outcomes are the result of outstanding collaboration between Ironwood and Forest, with both companies participating in these clinical trials. We look forward to further advancing the development of linaclotide, a novel product in a therapeutic category where patients have very limited treatment options.”

Peter Hecht, Chief Executive Officer of Ironwood, said, “We are very pleased to observe how well the top-line results of these larger Phase 3 trials replicate the effect of linaclotide observed in our Phase 2b trial.”

These two trials are part of Ironwood and Forest’s larger Phase 3 program investigating the effect of linaclotide treatment on patients with CC or irritable bowel syndrome with constipation (IBS-C). The companies are currently enrolling two additional pivotal Phase 3 trials in North America to assess the safety and efficacy of linaclotide in patients with IBS-C and expect results in the second half of calendar year 2010.

## Trial 01 Results

Trial 01 was conducted in 633 patients meeting modified Rome II criteria for CC. The trial included a two-week pretreatment baseline period and a 12-week treatment period. The primary efficacy endpoint was 12-week CSBM overall responder. A 12-week CSBM overall responder is a patient who had three or more CSBMs per week and an increase of at least one CSBM per week over baseline for at least nine of the 12 weeks of the treatment period. During the baseline period, 72 percent of patients had no CSBMs. Based on the intent-to-treat population:

- The 12-week CSBM overall responder rate was 16.0 percent in the 133 mcg linaclotide group ( $p=0.0012$ ) and 21.3 percent in the 266 mcg linaclotide group ( $p<0.0001$ ), a numerical increase of 2.6 and 3.5 fold, respectively, as compared to 6.0 percent in the placebo group. A total of 16.0 percent ( $p=0.0012$ ) of patients receiving 133 mcg and 21.8 percent ( $p<0.0001$ ) of patients receiving 266 mcg of linaclotide experienced  $\geq 3$  weekly CSBMs in at least nine out of 12 weeks as compared to 6.0 percent of patients receiving placebo. In addition 31.0 percent ( $p<0.0001$ ) of patients receiving 133 mcg and 40.1 percent ( $p<0.0001$ ) of patients receiving 266 mcg of linaclotide achieved an increase of  $\geq 1$  from baseline in weekly CSBMs in at least nine out of 12 weeks as compared to 13.0 percent of patients receiving placebo.
- Linaclotide-treated patients demonstrated a significant increase in average weekly CSBMs from baseline (0.6 for placebo; 2.0 for 133 mcg,  $p<0.0001$ ; 2.7 for 266 mcg,  $p<0.0001$ ) and a significant increase in average weekly spontaneous bowel movements (SBMs) from baseline (1.1 for placebo; 3.4 for 133 mcg,  $p<0.0001$ ; 3.7 for 266 mcg,  $p<0.0001$ ).

All secondary endpoints measured in Trial 01, which included those detailed in the previous paragraph as well as bloating, abdominal discomfort, stool consistency, straining, and constipation severity, were statistically significant ( $p<0.001$ ) for linaclotide versus placebo at both doses.

## Trial 303 Results

Trial 303, conducted in 643 patients, was identical to Trial 01 in design except Trial 303 also included a four-week randomized withdrawal period. During the baseline period, 68 percent of patients had no CSBMs. Based on the intent-to-treat population:

- The 12-week CSBM overall responder rate was 21.2 percent in the 133 mcg linaclotide group ( $p<0.0001$ ) and 19.4 percent in the 266 mcg linaclotide group ( $p<0.0001$ ), a numerical increase of 6.3 and 5.8 fold, respectively, as compared to 3.3 percent in the placebo group. A total of 21.7 percent ( $p<0.0001$ ) of patients receiving 133 mcg and 19.4 percent ( $p<0.0001$ ) of patients receiving 266 mcg of linaclotide experienced  $\geq 3$  weekly CSBMs in at least nine out of 12 weeks as compared to 3.8 percent of patients receiving placebo. In addition 39.2 percent ( $p<0.0001$ ) of patients receiving 133 mcg and 37.0 percent ( $p<0.0001$ ) of patients receiving 266 mcg of linaclotide achieved an increase of  $\geq 1$

from baseline in weekly CSBMs in at least nine out of 12 weeks as compared to 11.0 percent of patients receiving placebo.

- Linaclotide-treated patients demonstrated a significant increase in average weekly CSBMs from baseline (0.5 for placebo; 1.9 for 133 mcg,  $p < 0.0001$ ; 2.0 for 266 mcg,  $p < 0.0001$ ) and a significant increase in average weekly SBMs from baseline (1.1 for placebo; 3.0 for 133 mcg,  $p < 0.0001$ ; 3.0 for 266 mcg,  $p < 0.0001$ ).

All secondary endpoints measured in Trial 303, which included those detailed in the previous paragraph as well as bloating, abdominal discomfort, stool consistency, straining, and constipation severity, were statistically significant ( $p < 0.01$ ) for linaclotide versus placebo at both doses.

Across both trials, the most common adverse events in linaclotide-treated patients were diarrhea, flatulence, and abdominal pain. Overall rates of discontinuation due to adverse events were 7.4 percent for linaclotide and 4.2 percent for placebo.

The results of Trial 01 and Trial 303 were consistent with the previously reported CC Phase 2b trial in which weekly SBM was the primary endpoint. Once full analyses of the CC Phase 3 data have been completed, Ironwood and Forest expect to present detailed results at an appropriate scientific conference.

### About Linaclotide Doses

The doses of linaclotide referenced in previous public disclosures represented the total peptide content; however, moving forward the doses will be expressed as linaclotide content. The 150 and 300 mcg linaclotide referenced in prior public disclosures are equivalent to the 133 and 266 mcg linaclotide content referenced in this public disclosure and all public disclosures going forward.

### Glossary of Terms

**Spontaneous bowel movement (SBM):** An SBM is a bowel movement that occurs in the absence of laxative, enema, or suppository usage within the preceding 24 hours.

**Complete spontaneous bowel movement (CSBM):** A CSBM is an SBM that is accompanied by the patient self-reporting a feeling of complete emptying of the bowel.

### About Linaclotide

Linaclotide is an orally delivered peptide that acts locally in the gut with no detectable systemic exposure at therapeutic doses and is intended for once-daily administration. Linaclotide is an agonist of guanylate cyclase type-C (GC-C), a receptor found on the lining of the intestine. Activation of GC-C leads to increases in intracellular and extracellular cGMP. In preclinical models, extracellular cGMP inhibited afferent nerve firing and positively affected markers of abdominal pain, while intracellular cGMP led to activation of anion channels which stimulated anion and fluid secretion into the intestine, leading to accelerated intestinal transit. Linaclotide is a first-in-class compound in Phase 3 clinical development for the treatment of IBS-C and CC.

Linaclotide demonstrated proof of concept in a comprehensive Phase 2b program, comprised of two clinical studies in over 700 patients with either IBS-C or CC. In patients with IBS-C, linaclotide significantly reduced abdominal pain, abdominal discomfort, and bloating and improved bowel function throughout the 12-week treatment period. In patients with CC, linaclotide reduced constipation, abdominal discomfort, and bloating throughout the four-week treatment period. Across both studies, the most common and only dose-responsive adverse event in the linaclotide-treated groups was diarrhea, and diarrhea was the most common adverse event leading to discontinuation. All other adverse events occurred with similar frequency across the placebo and linaclotide dose groups. An issued composition of matter patent for linaclotide provides protection to 2025. In September 2007, Ironwood and Forest entered into a 50/50 collaboration to co-develop and co-promote linaclotide in the United States. In April 2009, Ironwood licensed to Almirall the European rights to develop and commercialize linaclotide.

### **About Chronic Constipation (CC)**

As many as 34 million Americans suffer from symptoms associated with CC and 8.5 million patients have sought treatment. Patients with CC often experience hard and lumpy stools, straining during defecation, a sensation of incomplete evacuation, and fewer than three bowel movements per week, as well as discomfort and bloating. This condition significantly affects patients' quality of life by impairing their ability to work and participate in typical daily activities. Half of patients are not satisfied with currently available treatments.

### **About Irritable Bowel Syndrome with Constipation (IBS-C)**

IBS-C is a chronic functional gastrointestinal disorder characterized by abdominal pain, discomfort, and bloating associated with altered bowel habits, and as many as 11 million people in the U.S. suffer from it. There are currently few available therapies to treat this disorder and there is a high rate of dissatisfaction with available therapies. Patients suffering from IBS-C can be affected physically, psychologically, socially, and economically.

### **About Ironwood Pharmaceuticals**

Ironwood Pharmaceuticals ([www.ironwoodpharma.com](http://www.ironwoodpharma.com)) is an entrepreneurial pharmaceutical company dedicated to the art and science of great drugmaking. Linaclotide, the Company's first-in-class compound, is being evaluated in a confirmatory Phase 3 program for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic constipation. Ironwood also has a growing pipeline of additional drug candidates in earlier stages of development. Ironwood has raised \$306 million in private equity financing and is located in Cambridge, Massachusetts.

### **About Forest Laboratories, Inc.**

Forest Laboratories (NYSE: FRX) is a U.S.-based pharmaceutical company with a long track record of building partnerships and developing and marketing products that make a positive difference in people's lives. In addition to its well-established franchises in therapeutic areas of

the central nervous and cardiovascular systems, Forest's current pipeline includes product candidates in all stages of development and across a wide range of therapeutic areas. The company is headquartered in New York, NY. To learn more about Forest Laboratories, visit [www.FRX.com](http://www.FRX.com).

*Except for the historical information contained herein, this release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements involve a number of risks and uncertainties, including the difficulty of predicting FDA approvals, the acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, the timely development and launch of new products, and the risk factors listed from time to time in Forest Laboratories' Annual Report on Form 10-K, Quarterly Report on Form 10-Q, and any subsequent SEC filings.*

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