



## **Ironwood and Forest Announce Positive Linaclotide Results from Second Phase 3 Trial in Patients with Irritable Bowel Syndrome with Constipation**

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

CAMBRIDGE, Mass. & NEW YORK, Nov 01, 2010 (BUSINESS WIRE) -- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) and Forest Laboratories, Inc. (NYSE: FRX) today announced positive top-line results from a 26-week Phase 3 clinical trial assessing the efficacy and safety of the investigational drug linaclotide in patients with irritable bowel syndrome with constipation (IBS-C). Analyses of the data indicate a statistically significant improvement ( $p < 0.0001$ ) was achieved for linaclotide-treated patients compared to placebo-treated patients on all four primary endpoints, which included two composite responder endpoints encompassing abdominal pain and complete spontaneous bowel movements (CSBMs), as well as individual responder endpoints for abdominal pain and CSBMs. Significant improvement ( $p < 0.001$ ) was also achieved for linaclotide-treated patients compared to placebo-treated patients on all pre-specified secondary endpoints, which were measures of abdominal pain, abdominal discomfort, bloating, and bowel symptoms. Both primary and secondary endpoints were assessed over the first 12 weeks of the treatment period, and these results were consistent with the first Phase 3 trial of linaclotide in patients with IBS-C.

Additionally, at each of the 26 weeks in the treatment period, mean changes from baseline in abdominal pain and CSBMs showed statistically significant improvements ( $p < 0.0001$ ) for linaclotide-treated patients compared to placebo-treated patients. The incidence of adverse events was similar to that observed in the first Phase 3 trial of linaclotide in patients with IBS-C, with diarrhea being the most common adverse event in linaclotide-treated patients.

"We are thrilled with the positive results from this trial, demonstrating a reduction in abdominal pain and an increase in CSBMs over the 26-week treatment period. Linaclotide's effect on these symptoms and tolerability profile has been remarkably consistent across the robust IBS-C and chronic constipation development program," said Peter Hecht, CEO of Ironwood. "We look forward to the opportunity to bring this promising treatment to the millions of individuals suffering from these chronic and highly bothersome gastrointestinal disorders."

"By successfully meeting all the primary and secondary endpoints in this trial, we now have two positive Phase 3 IBS-C trials and two positive Phase 3 chronic constipation trials," said Howard Solomon, Chairman and Chief Executive Officer of Forest Laboratories. "We look forward to filing the NDA for both indications in 2011."

This trial, MCP-103-302, is part of Ironwood and Forest's Phase 3 program investigating the effect of linaclotide treatment on patients with IBS-C or chronic constipation (CC). Previously, Ironwood and Forest reported positive results from the first of two Phase 3 trials in patients with IBS-C and two Phase 3 trials in patients with CC. The IBS-C trials were also designed to support regulatory submission in Europe. Today, in a separate press release, Ironwood and its European partner, Almirall, announced positive top-line results from this study for the E.U. endpoints.

#### **Trial MCP-103-302 Results**

Trial MCP-103-302 was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 805 patients meeting modified Rome II criteria for IBS-C. The trial included a two-week pretreatment baseline period and a 26-week treatment period with patients receiving a once-daily dose of linaclotide 266 mcg or placebo. Primary and secondary endpoints were assessed over the first 12 weeks of treatment. During the pretreatment baseline period, the mean abdominal pain score was 5.6 (on a 0 - 10 scale where 0 is no abdominal pain and 10 is very severe abdominal pain), with 87 percent of patients suffering abdominal pain every day and 76 percent having no CSBMs. The results for the four primary endpoints are detailed below.

#### **1. Composite responder endpoint 1: abdominal pain and CSBM**

-- A greater proportion of linaclotide-treated patients compared to placebo-treated patients (12.7 percent vs. 3.0 percent;  $p < 0.0001$ ) had, in the same week, at least a 30 percent reduction in abdominal pain, at least three CSBMs, and an increase of one or more CSBMs. These criteria had to be met for at least nine of the first 12 weeks of the treatment period for a patient to be considered a responder for composite responder endpoint 1.

#### **2. CSBM responder endpoint**

-- A greater proportion of linaclotide-treated patients compared to placebo-treated patients (18.0 percent vs. 5.0 percent;  $p < 0.0001$ ) had, in the same week, at least three CSBMs and an increase of one or more CSBMs. These criteria had to be met for at least nine of the first 12 weeks of the treatment period for a patient to be considered a responder and are

components of composite responder endpoint 1.

### 3. Abdominal pain responder endpoint

-- A greater proportion of linaclotide-treated patients compared to placebo-treated patients (38.9 percent vs. 19.6 percent;  $p < 0.0001$ ) had at least a 30 percent reduction in abdominal pain. This criterion had to be met for at least nine of the first 12 weeks of the treatment period for a patient to be considered a responder and is a component of composite responder endpoint 1.

### 4. Composite responder endpoint 2: abdominal pain and CSBM

-- A greater proportion of linaclotide-treated patients compared to placebo-treated patients (33.7 percent vs. 13.9 percent,  $p < 0.0001$ ) had, in the same week, at least a 30 percent reduction in abdominal pain and an increase of one or more CSBMs. These criteria had to be met for at least six of the first 12 weeks of the treatment period for a patient to be considered a responder for composite responder endpoint 2. This primary endpoint reflects the Food and Drug Administration (FDA) draft guidance published in March 2010 for evaluating the efficacy of IBS therapies.

All secondary endpoints demonstrated statistically significant ( $p < 0.001$ ) improvements for linaclotide-treated patients compared to placebo-treated patients. These endpoints include change from baseline measures of abdominal pain, abdominal discomfort, bloating, percent pain-free days, CSBM frequency, SBM frequency, stool consistency, and straining, as well as the individual components of composite responder endpoint 2 (abdominal pain responder and CSBM responder) as described below.

- For the abdominal pain component of composite responder endpoint 2, a greater proportion of linaclotide-treated patients compared to placebo-treated patients (48.9 percent vs. 34.5 percent,  $p < 0.0001$ ) had at least a 30 percent or greater reduction in pain for at least six of the first 12 weeks of the treatment period.
- For the CSBM component of composite responder endpoint 2, a greater proportion of linaclotide-treated patients compared to placebo-treated patients (47.6 percent vs. 22.6 percent,  $p < 0.0001$ ) had an increase of one or more CSBMs for at least six of the first 12 weeks of the treatment period.

The most common adverse events that occurred more frequently in linaclotide-treated patients compared to placebo-treated patients throughout the 26-week treatment period were diarrhea (19.7 percent vs. 2.5 percent), abdominal pain (4.5 percent vs. 4.0 percent), flatulence (3.7 percent vs. 2.2 percent), viral gastroenteritis (3.7 percent vs. 2.2 percent), and headache (3.2 percent vs. 2.7 percent). Overall rates of discontinuation due to adverse events were 10.2 percent for the linaclotide-treated patients and 2.5 percent for the placebo-treated patients; 4.5 percent of linaclotide-treated patients discontinued due to diarrhea compared with 0.2 percent of placebo-treated patients.

The companies expect to present detailed results at appropriate scientific conferences.

### New Drug Application (NDA) Timing

The companies expect to submit an NDA to the FDA for both the IBS-C and CC indications in the third quarter of calendar year 2011. The projected timeline is driven by commitments to exceed International Conference on Harmonisation (ICH) guidelines for the number of IBS-C and CC patients in long-term safety studies, conduct pre-NDA meetings with the FDA, and complete drug product stability studies to support a room temperature product for patients.

### Glossary of Terms

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

**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.

**ROME II Criteria:** A patient who reports abdominal discomfort or pain for two or more of the following three features for at least 12 weeks, which need not be consecutive, in the 12 months before the screening visit, or before starting chronic treatment with tegaserod or lubiprostone: (1) relieved with defecation; (2) onset associated with a change in frequency of stool; (3) onset associated with a change in form (appearance) of stool.

### About Linaclotide

Linaclotide, an investigational drug, is an agonist of the guanylate cyclase type-C (GC-C) receptor located on the luminal surface of the intestine. In preclinical models, linaclotide has been shown to reduce visceral pain, increase fluid secretion, and accelerate intestinal transit. The effects on secretion and transit are mediated through cyclic guanosine monophosphate (cGMP), which is also believed to modulate the activity of local nerves to reduce pain. Linaclotide is an orally delivered peptide that acts locally in the gut with no measurable systemic exposure at therapeutic doses and is intended for once-daily administration. Linaclotide is in Phase 3 clinical development for the treatment of irritable bowel syndrome with constipation

(IBS-C) and chronic constipation. An issued composition of matter patent for linaclotide provides protection to 2025. Ironwood and Forest are co-developing and will co-promote linaclotide in the United States. Ironwood has out-licensed linaclotide to Almirall for European development and commercialization, and to Astellas Pharma Inc. for development and commercialization in Japan, Indonesia, Korea, the Philippines, Taiwan, and Thailand.

#### 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 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. There is a high rate of dissatisfaction with currently available treatments.

#### About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is an entrepreneurial pharmaceutical company dedicated to the art and science of great drugmaking. Linaclotide, Ironwood's GC-C agonist, 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 is located in Cambridge, Mass. To learn more about Ironwood Pharmaceuticals, visit [www.ironwoodpharma.com](http://www.ironwoodpharma.com).

#### About Forest Laboratories, Inc.

Forest Laboratories' (NYSE: FRX) longstanding global partnerships and track record developing and marketing pharmaceutical products in the United States have yielded its well-established central nervous system and cardiovascular franchises and innovations in anti-infective medicine. The Company's pipeline, the most robust in its history, includes product candidates in all stages of development across a wide range of therapeutic areas. The Company is headquartered in New York, NY. To learn more, visit [www.FRX.com](http://www.FRX.com).

*This press release contains forward looking statements relating to the joint development efforts being undertaken by Forest and Ironwood with respect to the development of the pharmaceutical product linaclotide. Investors are cautioned not to place undue reliance on these forward- looking statements, including, but not limited to, our top-line assessment of our Phase 3 IBS-C clinical trial data and its implications for the future development of linaclotide, linaclotide's potential as a treatment for IBS-C, the successful completion of our long-term safety studies, our ability to produce an adequate commercial supply of linaclotide, the timing of our filing of a New Drug Application with the FDA for linaclotide, and the potential size of linaclotide's target patient population. 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 the risks that our other joint linaclotide development activities do not progress as expected, serious adverse events arise in patients that are deemed to be definitely or probably related to linaclotide treatment, the incidence or severity of diarrhea in patients treated with linaclotide is higher than expected, and we are unable to produce an adequate commercial supply of linaclotide, as well as risks related to the difficulty of predicting FDA approvals, the acceptance of and demand for new pharmaceutical products, the impact of competitive products and pricing, and whether linaclotide will ever be commercialized successfully. In addition, both Forest and Ironwood (and their respective contributions to the development of linaclotide) may be affected by the risks that are listed in each of their Quarterly Reports on Form 10-Q for the quarter ended June 30, 2010, in addition to those that are listed from time to time in their Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and other SEC filings. Neither Forest nor Ironwood undertakes any obligation to update these forward-looking statements to reflect events or circumstances occurring after this press release. These forward-looking statements speak only as of the date of this press release. All forward-looking statements are qualified in their entirety by this cautionary statement.*

SOURCE: Forest Laboratories, Inc. & Ironwood Pharmaceuticals, Inc.

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