Almirall and Ironwood announce positive results from the second Phase III trial of linaclotide in patients with irritable bowel syndrome with constipation

- **Top-line results from the second of two Phase III linaclotide trials show that both co-primary and all secondary efficacy endpoints were met**
- **Almirall will now move forward with regulatory filing in Europe for linaclotide in second half 2011**

Barcelona and Cambridge, Mass., November 1, 2010 — Almirall, S.A. (ALM:MC) and Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) today announced positive top-line results from a 26-week pivotal Phase III clinical trial assessing the efficacy and safety of once-daily dosing of linaclotide 266 mcg in patients with irritable bowel syndrome with constipation (IBS-C).

The two co-primary endpoints required by the European Medicines Agency (EMA) were met in this trial, showing statistically significant improvements for linaclotide-treated patients for both abdominal pain/abdominal discomfort responder ($p<0.0001$) and IBS degree of relief responder ($p<0.0001$) over the first 12 weeks. Significant improvement was also achieved for all secondary efficacy endpoints ($p<0.0001$) including 26-week abdominal pain/abdominal discomfort responder, 26-week IBS degree of relief responder, and change from baseline in 12-week stool frequency, stool consistency, straining and bloating. The incidence of adverse events was similar to that observed in the previous Phase III trial of linaclotide in patients with IBS-C, with diarrhoea being the most common adverse event in linaclotide-treated patients.

"*These very positive results represent a significant milestone in the Phase III clinical trial programme for linaclotide which has been developed specifically to provide long term relief from the symptoms of irritable bowel syndrome with constipation, an area in which a very high unmet need exists*," said Per Olof Andersson, Chief Scientific Officer, Almirall.

"We continue to see that linaclotide significantly improves abdominal pain and constipation symptoms. The results of these Phase III data show that patients with IBS-C experienced sustained improvement of their symptoms over 26 weeks," said Mark Currie, Ph.D, Chief Scientific Officer, Ironwood. "We are looking forward to the opportunity to bring this treatment to the millions of patients suffering from IBS-C globally."

This trial, MCP-103-302, conducted in North America jointly by Ironwood and its U.S. partner Forest Laboratories, Inc., was designed to support regulatory submission for linaclotide in both Europe and the U.S. In a separate press release issued today, Ironwood and Forest announced positive top-line results from this trial for the U.S. endpoints.

Ironwood has out-licensed linaclotide to Almirall for European development and commercialization. Regulatory filing in Europe is expected in the second half of 2011. The companies expect to present detailed results of the two Phase III trials at appropriate scientific conferences.

Phase III Trial MCP-103-302

Primary Efficacy Endpoint 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 pre-treatment baseline period and a 26-week treatment period, with patients receiving either a once-daily dose of linaclotide 266 mcg or placebo. During the pre-treatment 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 from abdominal pain every day. The results for the co-primary endpoints are detailed below:

1. **12-week abdominal pain/abdominal discomfort responder**
   A greater proportion of linaclotide-treated patients compared to placebo-treated patients (54.1 percent vs. 38.5 percent, $p<0.0001$) had an improvement from baseline of 30 percent or more in either the mean abdominal pain score or the mean abdominal discomfort score for at least six of the first 12 weeks of the 26-week treatment period, with neither of these scores worsening from baseline for the same week.

2. **12-week IBS degree of relief responder**
   A greater proportion of linaclotide-treated patients compared to placebo-treated patients (39.4 percent vs. 16.6 percent, $p<0.0001$) responded to the degree of relief of IBS symptoms question with an answer of “considerably relieved” or “completely relieved”, for at least six of the first 12 weeks of the 26-week treatment period.

Main Secondary Endpoints

All main secondary endpoints measured in MCP-103-302 were statistically significant ($p<0.0001$) for linaclotide-treated patients compared to placebo-treated patients: 26-week abdominal pain/ abdominal discomfort responder (53.6 percent vs. 36.0 percent), 26-week IBS degree of relief responder (37.2 percent vs. 16.9 percent), and changes from baseline over 12 weeks in stool frequency, stool consistency, straining, and bloating.

Adverse Events

The most common adverse events that occurred more frequently in linaclotide-treated patients compared to placebo-treated patients were diarrhoea (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 linaclotide-treated patients and 2.5 percent for placebo-treated patients; 4.5 percent of linaclotide-treated patients discontinued due to diarrhoea compared with 0.2 percent of placebo-treated patients.

About Almirall

Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, Spain, it researches, develops, manufactures and commercializes its own R&D and licensed drugs with the aim of improving people’s health and wellbeing.

Almirall focuses its research resources on therapeutic areas related to the treatment of asthma, COPD (Chronic Obstructive Pulmonary Disease), rheumatoid arthritis, multiple sclerosis, psoriasis and other dermatological conditions.

Almirall’s products are currently present in over 70 countries while it has direct presence in Europe and Latin America through 12 affiliates.

For further information please visit the website at: www.almirall.com

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 III 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. For further information, please visit www.ironwoodpharma.com.

This press release contains forward looking statements. 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 III 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 the filing of a Marketing Authorization Application 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 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 diarrhoea 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 regulatory 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. Applicable risks also include those that are listed in our Quarterly Report on Form 10-Q for the three months ended June 30, 2010, in addition to the risk factors that are listed from time to time in Ironwood Pharmaceuticals' Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and any subsequent SEC filings. We undertake no 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.

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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 III 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. Also, 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

Irritable bowel syndrome (IBS), a functional gastrointestinal disorder, is a recognized complex symptom with abdominal pain and disturbed bowel action. It leads to a substantial reduction in quality of life, accompanied by considerable socio-economic and psychological consequences[1-4], and represents a major proportion of gastrointestinal workload in both primary and secondary care[5]. The overall prevalence is 11.5 percent (6.2 percent–12 percent); 9.6 percent have current symptoms, 4.8 percent have been formally diagnosed, with 16-34% of these patients experiencing the constipation-predominant form of the condition [6].

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 the Prior Phase III Trial

Results communicated in this release are consistent with those from a prior Phase III trial assessing linaclotide's safety and efficacy in patients with IBS-C. Positive top-line results from the Phase III clinical trial LIN-MD-31, which involved 803 patients and assessed the efficacy and safety of a once-daily dosing of linaclotide 266 mcg in patients with irritable bowel syndrome with constipation, was announced in September 2010.[7]

References

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