

Linacotide Receives Positive CHMP Opinion for the Treatment of IBS-C

- Linacotide is a first-in-class therapeutic option for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adult patients-
- In two pivotal Phase III studies evaluating its efficacy and safety in IBS-C in adults, linacotide was found to significantly improve abdominal pain/discomfort and relief of other IBS-C symptoms^{i,ii} -
- Almirall holds exclusive marketing rights for linacotide in Europe-

BARCELONA, Spain & CAMBRIDGE, Mass.--(BUSINESS WIRE)-- [Almirall, S.A.](#) (ALM:MC) and [Ironwood Pharmaceuticals, Inc.](#) (NASDAQ: IRWD) announced today that the European Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion recommending the marketing approval for Constella[®] (linacotide 290 micrograms), for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

The CHMP positive opinion is a recommendation to the European Commission (EC) and one of the final steps in the review of a marketing authorization application. The EC usually follows the recommendations of the CHMP. Once approved, it will be marketed under the brand name Constella[®].

"Patients with IBS-C suffer from several very uncomfortable gastrointestinal symptoms for which there are currently very few available therapies", said Bertil Lindmark, Chief Scientific Officer at Almirall. "With linacotide physicians will have one of the first specifically designed therapies with proven efficacy and tolerability over time. Therefore, we are very pleased at Almirall with this first IBS-C treatment recommended for approval by CHMP and are confident in linacotide's benefits".

This positive recommendation is based on the efficacy and safety of linacotide evaluated in two double-blind, placebo-controlled Phase III clinical studies. The clinical trials involved approximately 1,600 adult patients, of which more than 800 were treated with linacotide 290 mcg. In both trials, treatment with linacotide resulted in statistically significant improvements in both abdominal pain/discomfort and degree of relief of IBS-C symptoms (co-primary endpoints), as well as complete spontaneous bowel movement frequency, stool consistency and severity of straining and bloating (secondary endpoints). These improvements were maintained over the entire treatment period (12 and 26 weeks). The incidence of adverse events was similar in both studies, with diarrhoea being the most common adverse event in linacotide-treated patients^{i, ii}.

"This positive opinion is a significant step toward helping these highly symptomatic adult patients; many of whom are searching for new treatment options," said [Mark Currie, PhD, Senior Vice President, R&D and Chief Scientific Officer](#) of Ironwood. "The discovery of linacotide by Ironwood scientists and the work we have done to reach patients in Europe with our partner, Almirall, has been a collaborative effort with the goal of helping this underserved patient population."

Almirall holds exclusive marketing rights for linacotide in Europe.

About linacotide (Constella[®])

Linacotide is a guanylate cyclase-C agonist (GCCA) that is provided as an oral capsule intended for once-daily administration for the treatment of irritable bowel syndrome with constipation.

It binds to guanylate cyclase C locally in the intestine, with no measurable blood plasma concentrations, resulting in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevations in intracellular cGMP are believed to stimulate secretion of intestinal fluid and accelerate gastrointestinal transit resulting in increased frequency of bowel movements. Elevations in extracellular cGMP are believed to decrease activity of pain-sensing nerves, which is thought to be responsible for a reduction in intestinal pain, according to nonclinical models.

Constella[®] is a trademark owned by Ironwood Pharmaceuticals, Inc. and its use in Europe is pending marketing approval from the European Commission.

About Irritable Bowel Syndrome with Constipation (IBS-C)

IBS is defined as a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit and with features of disordered defecation.ⁱⁱⁱ IBS-C is one of four clinically different subtypes of IBS. One-third of patients with IBS are thought to have IBS-C^{iv} and suffer chronically from both abdominal pain and constipation.

The Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders includes criterion for the diagnosis of IBSⁱⁱⁱ as:

- Recurrent abdominal pain or discomfort at least three days/month, in the last three months with symptom onset at least 6 months prior to diagnosis, associated with two or more of the following:
 - improvement with defecation
 - onset associated with a change of frequency of stool
 - onset associated with a change in form (or appearance) of stool

The estimated prevalence of IBS at 10-15% of the European population puts it in line with conditions such as migraine (12%) and asthma (11%).^v IBS can have a negative impact on daily living with considerable socio-economic and psychological consequences, and represents a major proportion of gastrointestinal workload in both primary and secondary care. Due to the complex, multimodal nature of the condition there is no cure for IBS and minimal therapeutic options.^{vi}

About Almirall

Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, it researches, develops, manufactures and commercialises its own R&D and licensed drugs with the aim of improving people's health and wellbeing. Almirall focuses its research resources on respiratory, gastrointestinal, dermatology and pain. Almirall's products are currently present in over 70 countries in the five continents. With the opening of the Canadian affiliate, Almirall has now direct presence in Europe, Mexico and Canada through 13 affiliates. For further information please visit: www.almirall.com

About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is an entrepreneurial pharmaceutical company dedicated to the art and science of great drugmaking. Ironwood is located in Cambridge, Mass. To learn more, 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, the anticipated approval for marketing authorization by the European Medicines Agency (EMA), the potential indication and patient population for linaclotide and the anticipated brand name 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 the risks that the EMA does not grant marketing authorization for linaclotide, the EMA does not approve the brand name Constella®, serious adverse events arise in patients that are deemed to be definitely or probably related to linaclotide treatment, and the incidence or severity of diarrhea in patients treated with linaclotide is higher than expected, as well as risks related to the difficulty of predicting regulatory approvals. Applicable risks also include those that are listed in Ironwood Pharmaceuticals' Quarterly Report on Form 10 - Q for the quarter ended June 30, 2012, 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.

References

ⁱ E.M. Quigley, A.J. Lembo, C. Diaz, et al. Significant improvements in abdominal pain and bowel symptoms in a phase 3 trial of linaclotide in patients with irritable bowel syndrome with constipation (IBS-c): A european perspective. Gut 2011; 60 (Suppl 3) A80.

ⁱⁱ A.J. Lembo, J. Fortea, C. Diaz, et al. 26-Week Efficacy and safety of once-daily oral linaclotide in patients with irritable bowel syndrome with constipation: a european perspective. Gut 2011; 60 (Suppl 3) A41.

ⁱⁱⁱ Longstreth GF, Thompson WG, Chey WD et al. - Functional Bowel Disorders. Gastroenterology 2006; 130: 1480-1491

^{iv} American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the

management of irritable bowel syndrome. *Am J Gastroenterol* 2009; 104 Suppl 1:S1-35

^v P. S. Hungin et al - The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects - *Aliment Pharmacol Ther* 2003; 17: 643—650.

^{vi} Camilleri M, Chang L. - Challenges to the therapeutic pipeline for irritable bowel syndrome: end points and regulatory hurdles. *Gastroenterology* 2008;135:1877—1891

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