Linaclotide provides long term relief from the symptoms of irritable bowel syndrome with constipation[i]

- **Full results from two Phase III linaclotide trials involving over 1,600 patients with irritable bowel syndrome with constipation (IBS-C) presented at the European Gastroenterology Week (UEGW) congress in Stockholm**
- **Linaclotide demonstrated significant improvement in abdominal pain/discomfort and degree of relief as well as quality of life[ii,iii]**
- **The estimated prevalence of IBS is 10-15% in the European population putting it in line with higher profile conditions such as migraine (12%) and asthma (11%).[iv]**

Stockholm, Sweden, 24th October 2011 — Almirall, S.A. (ALM.MC) announced today that full results from two pivotal Phase III clinical trials assessing the efficacy and safety of once-daily dosing of linaclotide 290 mcg in patients with IBS-C are presented at the 19th European Gastroenterology Week (UEGW) congress showing that linaclotide significantly improved abdominal pain/discomfort and relieved IBS-C symptoms.

The impact of linaclotide on patients' quality of life from baseline to 12 weeks was measured using the Irritable Bowel Syndrome – Quality of Life Questionnaire (IBS-QoL). Pooled data from the two Phase III trials show that linaclotide statistically significantly improved IBS-QoL overall scores and seven out of eight important QoL domains (dysphoria, body image, health worry, sexual relationships, food avoidance and social reaction) compared with placebo in adults with IBS-C ($p<0.001$). The data also demonstrate that the proportion of patients meeting responder criteria for a ≥10-point or ≥14-point change from baseline was statistically significantly greater for patients treated with linaclotide versus placebo at week 12 for the IBS-QoL overall and all eight subscale scores ($p<0.05$).

"Results from the Phase III trials show that linaclotide provided relief for up to 26 weeks from the symptoms of irritable bowel syndrome with constipation, Importantly in these studies linaclotide had a favourable safety profile." said Anthony Lembo, Associate Professor of Medicine, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, USA

Bertil Lindmark, Chief Scientific Officer at Almirall commented: *"IBS-C is an underserved area of gastrointestinal medicine and linaclotide shows great promise as the first targeted therapy. We are excited by the prospect of being able to help patients suffering of this disease."*

Also, a total of 8 abstracts (3 posters, 5 oral presentations) are presented during the congress. The titles and presentation times are summarized below:

Session Date: 24/10/11 - Session Room: Poster Area
Abstract No: P0497
ASSESSING GLOBAL CHANGE AND SYMPTOM SEVERITY IN SUBJECTS WITH IRRITABLE BOWEL SYNDROME: QUALITATIVE ITEM TESTING - **J Johnston**, S Fehnel, CB Kurtz, A Mangel

Abstract No: P0501
RAT INTESTINAL METABOLISM OF LINACLOTIDE, A THERAPEUTIC AGENT IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME WITH CONSTIPATION - **MM Kessler**, RW Busby, JD Wakefield, WP Bartolini, AP Bryant, JV Tobin, EA Cordero, A Fretzen, CB Kurtz, MG Currie

Abstract No: P0503
TWO RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 TRIALS OF LINACLOTIDE IN ADULTS WITH IRRITABLE BOWEL SYNDROME: EFFECTS ON QUALITY OF LIFE - **RT Carson**, S Tourkodimitris, BE Lewis, JM Johnston

Session Date: 24/10/11 - Presentation Time: 16.21:16.33 - Session Room: K2
Abstract No: OP120
EXTRACELLULAR CGMP HAS CONTRASTING EFFECTS ON COLONIC AFFERENT MECHANOSENSITIVITY IN CONTROL AND TNBS-TREATED MICE - J Castro, PA Hughes, CM Martin, A Silos-Santiago, C Kurtz, **LA Blackshaw**, SM Brierley

Session Date: 25/10/11 - Presentation Time: 09.30-09.42 - Session Room: K21
Abstract No: OP173
LINACLOTIDE SIGNIFICANTLY IMPROVES POST-OPERATIVE ILEUS AND OPIATE-INDUCED CONSTIPATION IN RATS - **AP Bryant**, EA Cordero, JV Tobin, S Rivers, CB Kurtz, MG Currie

Session Date: 25/10/11 - Presentation Time: 09.42-09.54 - Session Room: K21
Abstract No: OP174
26-WEEK EFFICACY AND SAFETY OF ONCE-DAILY ORAL LINACLOTIDE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH CONSTIPATION: A EUROPEAN PERSPECTIVE - AJ Lembo, J Fortea, C Diaz, M Falques, JZ Shao, BJ Lavins, HA Schneier, JM Johnston

Session Date: 26/10/11 - Presentation Time: 09.14-09.26 - Session Room: A8/A9
Abstract No: OP350
LINACLOTIDE, A NOVEL PEPTIDE IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME WITH CONSTIPATION (IBS-C), IS DIGESTED IN THE MOUSE AND HUMAN SMALL INTESTINE TO SMALL PEPTIDES - MM Kessler, RW Busby, JD Wakefield, WP Bartolini, P Germano, AP Bryant, CB Kurtz, MG Currie

Session Date: 26/10/11 - Presentation Time: 09.26-09.38 - Session Room: A8/A9
Abstract No: OP351
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 - EM Quigley, AJ Lembo, C Diaz, J Fortea, M Falques, S Shiff, KShi,
HA Schneier, JM Johnston

Almirall submitted a Marketing Authorisation Application to the European Medicines Agency for linaclotide for the treatment of IBS-C in September 2011. Once approved, linaclotide will be marketed in Europe under the trademark Constella®.

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About the Phase III studies
The two co-primary endpoints required by the European Medicines Agency (EMA) were met in both Phase III trials, showing statistically significant improvements for linaclotide-treated patients for both abdominal pain/abdominal discomfort responder ($p<0.001$) and IBS degree of relief responder ($p<0.001$) 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. Diarrhoea was the most common adverse event reported by linaclotide-treated patients and was generally mild to moderate in severity. Linaclotide improves the complete spontaneous bowel movement (CSBM) frequency, stool consistency, straining, abdominal pain, bloating and abdominal discomfort within the first week and the effect was sustained throughout a 26-week treatment period.

About Linaclotide
Linaclotide, a first-in-class 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 reduced visceral hypersensitivity, increased fluid secretion, and accelerated 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.

Ironwood Pharmaceuticals, Inc. and Forest Laboratories, Inc. are co-developing and, if approved, will co-promote linaclotide in the United States. Ironwood has out-licensed linaclotide to Almirall for European development and commercialisation and to Astellas Pharma Inc. for development and commercialisation in Japan, Indonesia, Korea, the Philippines, Taiwan and Thailand.

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'.[v]

The Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders includes criterion for the diagnosis of IBS,[vi] as:

- Recurrent abdominal pain or discomfort at least three days/month, in the last three months, 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 this disease in line with higher profile conditions such as migraine (12%) and asthma (11%).[vii] It leads to a substantial reduction in quality of life, accompanied by considerable socio-economic and psychological consequences[iv,v] and represents a major proportion of gastrointestinal workload in both primary and secondary care[ix].

Owing to the complex, multimodal nature of the condition there is no cure for IBS and no 'gold standard' of treatment.[viii] Irritable bowel syndrome with constipation (IBS-C) is one of four clinically different subtypes of IBS. One third of patients with IBS are thought to have IBS-C, [v,vi,ix] and therefore live with both abdominal pain and constipation.

About Almirall
Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, Spain, 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 therapeutic areas related to the treatment of asthma, COPD (Chronic Obstructive Pulmonary Disease), gastrointestinal disorders, 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.

References

[i] Carson T. et al – Two randomised, double-blind, placebo-controlled Phase 3 trials of linaclotide in adults with irritable bowel syndrome: effects on quality of life. European Gastroenterology Week, 22-16 October 2011, Stockholm abstract#: P0503

[ii] Lembo A. et al – 26-week efficacy and safety of once-daily oral linaclotide in patients with irritable bowel syndrome with constipation: a European perspective. European Gastroenterology Week, 22-16 October 2011, Stockholm abstract#: OP174

[iii] Quigley E. 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. European Gastroenterology Week, 22-16 October 2011, Stockholm abstract#: OP351

[iv] 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.

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

[vi] Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders

[vii] 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.

[viii] Camilleri M, Chang L. - Challenges to the therapeutic pipeline for irritable bowel syndrome: end points and regulatory hurdles. *Gastroenterology* 2008;135:1877–1891

[ix] 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