

POINT OF VIEW

# Linaclotide in the treatment of patients with irritable bowel syndrome and constipation - analysis of an opportunity

Fernando Carballo

*Comisión de Excelencia Clínica within Sociedad Española de Patología Digestiva (SEPD). Department of Digestive Diseases. Unidad de Gestión Clínica de Digestivo. University Hospital "Virgen de la Arrixaca". Instituto Murciano de Investigación Biosanitaria (IMIB). Murcia, Spain*

## ABSTRACT

Linaclotide is a secretagogue that provides a combined effect on visceral pain. The European Medicines Agency has authorized its indication for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation in adults. The purpose of this review is to discuss the clinical framework for linaclotide use in our setting, the drug's characteristics and pre-clinical development, and the clinical studies supporting its use in order to establish relevant views regarding its validity and clinical applicability. The results suggest that the only —non-severe— adverse effect associated with this drug is diarrhea. As regards effectiveness, linaclotide consistently shows favorable, significant differences in absolute risk *versus* placebo for all objective outcome variables described by regulatory agencies, with a combined pain and constipation response between 12.6% and 22.8% according to the variable and trial under consideration. This response is sustained and drug-related, as it goes away upon discontinuation. To conclude, linaclotide has a safety and efficacy profile that, from a clinical perspective, warrants its use for patients meeting irritable bowel syndrome and constipation criteria, with significant symptoms that cannot be relieved with other less specific measures. In the absence of predictive rules for response, it is recommended that, should the patient fail to respond, he or she should be considered not eligible for linaclotide therapy, and both indication and treatment continuity should be reserved for objective responders alone.

**Key words:** Irritable bowel syndrome. Constipation. Visceral pain.

---

Carballo F. Linaclotide in the treatment of patients with irritable bowel syndrome and constipation - analysis of an opportunity. *Rev Esp Enferm Dig* 2013;105:345-354.

---

Received: 12-06-2013  
Accepted: 26-06-2013

**Correspondence:** Fernando Carballo. Department of Digestive Diseases. Hospital Clínico Universitario Virgen de la Arrixaca. Carretera Madrid-Cartagena, s/n. 30120 El Palmar, Murcia. Spain  
e-mail: luisf.carballo@carm.es

## ABBREVIATIONS

cGMP: Cyclic guanosine monophosphate.  
CT: Clinical trial.  
EMA: European Medicines Agency.  
FDA: Food and Drug Administration.  
GC-C: Guanylate cyclase C.  
IBS: Irritable bowel syndrome.  
IBS-C: Irritable bowel syndrome with constipation.  
IBS-D: Irritable bowel syndrome with diarrhea.  
IBS-M: Irritable bowel syndrome, mixed type.  
IBS-QOL: Irritable Bowel Syndrome-Quality of Life.  
NNT: Number needed to treat.  
SEPD: Sociedad Española de Patología Digestiva.

## INTRODUCTION

Linaclotide is a guanylate cyclase type-C receptor agonist approved by the European Medicines Agency (EMA) for the symptomatic treatment of adults with moderate to severe irritable bowel syndrome and constipation (1).

IBS-C is a complex health issue regarding its pathogenesis and pathophysiology, as well as its clinical conceptualization and diagnostic borders (2). Current management is of reduced effectiveness, and the benefit-risk ratio of early 5-HT<sub>3</sub> antagonists and 5-HT<sub>4</sub> agonists has limited their clinical use (3). Linaclotide is a novel drug that explores a mechanism of action different from those previously assayed, and is therefore a first-in-class drug.

The goal of this manuscript is to review the clinical framework for linaclotide use in our setting, and to discuss the drug's characteristics and preclinical development, as well as the clinical studies supporting its use, in order to establish the appropriate judgments regarding their validity and the clinical applicability of their results.

## CLINICAL FRAMEWORK OF APPLICATION

Patients with irritable bowel syndrome (IBS) are divided, according to the Rome III criteria presently in force (Table I), into four subtypes: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS mixed type (IBS-M), and IBS not otherwise specified (4).

An excellent meta-analysis estimates a worldwide prevalence of 15% for IBS, which boils down to 9% when only patients with persistent symptoms for at least 12 months are considered (5), and more inconsistent or milder forms are therefore excluded. This same meta-analysis sets a proportion of 22% for the IBS-C subtype with respect to overall IBS (5). Overall prevalences between 13.6% (6) and 3.9% have been described for IBS in Spain, using Rome II criteria in the latter case (7). The most recent Spanish study, using Rome III criteria, reveals an intermediate percentage at 8.3% (8). IBS induces a high demand for health care (9), high costs, absenteeism, and reduced quality of life (3,10-14). Regarding the IBS-C subtype in the European setting, a systematic review including Spain, and a recent study in France, Italy and the UK confirm the significant impact of this disease, suggesting that improved management would offer significant improvements in health status and socio-economic costs (3,15).

The pathogenetic mechanisms involved in IBS include motility disorders, visceral hypersensitivity, lymphocyte, cytokine, and mast cell-mediated inflammation, the presence of prior intestinal infections, changes in microflora, bacterial overgrowth, food hypersensitivity, carbohydrate malabsorption, gluten intolerance, genetic factors, and

**Table I. Rome III diagnostic criteria and subtypes for irritable bowel syndrome (taken from reference no. 4)**

### *Diagnostic criteria\**

Recurrent abdominal pain or discomfort for at least 3 days within the last 3 months in association with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in stool frequency
- Onset associated with a change in stool form (appearance)
- Inicio asociado con un cambio en la forma (aparición) de las heces

### *IBS subtypes (Bristol scale recommended for stool consistency):*

- IBS with constipation when at least 25% of stools are hard and fewer than 25% are loose or watery
- IBS with diarrhea when at least 25% of stools are loose or watery and fewer than 25% are hard
- IBS mixed type when at least 25% of stools are loose or watery and at least 25% are hard
- IBS not otherwise specified when changes in stool consistency do not fit any of the previous subtypes

\*Criteria that must be met in the last 3 months with symptom onset at least 6 months before diagnosis.

psychosocial dysfunction. This high variety of pathophysiological approaches is logically reflected in a host of therapeutic alternatives of limited effectiveness, as discussed above. General measures should underscore an adequate clinico-therapeutic relationship regarding patient education, physical activity, and psychosocial approach. Most common among food modifications is the use of dietary fiber, but also lactose exclusion, malabsorption studies for other carbohydrates, discontinuation of gas-producing foods, and even dietary manipulation to exclude potential allergens in some cases. The use of probiotics and of antibiotics like rifaximin has also been posited. As regards drug therapies, the classical approach includes using spasmolytics, antidepressants, and laxatives or antidiarrheals according to IBS subtype. Within such classic approaches, spasmolytics have proven superior to placebo both in a meta-analysis (16) and in a recent clinical trial (CT) of otilonium bromide (17). Another meta-analysis also suggests a significant benefit of antidepressants (18), which may induce neuromodulation and have pain-killing properties independent from their primary action. Regarding antidiarrheals, evidence is poorer and indicates stool frequency and consistency benefits but no overall improvement (19-21). This is similar to fecal bulk expanders and laxatives, which may improve constipation but not overall symptoms (22).

Regarding IBS management with molecules to modulate visceral hypersensitivity, 5-HT<sub>3</sub> antagonists have proven effective, particularly in women and the diarrheal subtype (23); however, one of these antagonists, alosetron, was associated with ischemic colitis and serious constipation induction. As for 5-HT<sub>4</sub> agonists, which may stimulate colonic motility, both tegaserod and renzapride have also proven effective for IBS symptom relief, specifically in IBS-C, but both have similarly been associated with ischemic colitis, and tegaserod also with other serious cardiovascular adverse events (3).

Finally, among secretagogues, besides linaclotide only lubiprostone -not available in Europe- has been tried for IBS-C, and seen to w abdominal pain and to improve constipation significantly (24-26).

## LINACLOTIDE CHARACTERISTICS AND PRECLINICAL DEVELOPMENT

As discussed above, linaclotide is a GC-C receptor agonist, with GC-C being an enzyme expressed in the luminal surface of intestinal epithelial cells that can synthesize cyclic guanosine monophosphate (GMPc). GMPc is a ubiquitous second messenger that —among many other physiological function— stimulates intestinal secretion (27). Early discovered natural activator ligands of GC-C included thermostable enterotoxins from *Escherichia coli*, followed by guanylin as first endogenous ligand (28). Linaclotide is a most potent thermostable enterotoxin homologue that is highly resistant to proteolytic degrada-

dation (27). During the development of linaclotide, this enzyme was seen to be the molecular target mediating all drug-related effects in experimental models using GC-C knockout mice (28).

Pharmacokinetic studies using *in vivo* experimental rat models show that linaclotide is only minimally absorbed (29), which was confirmed during clinical development and ensures low toxicity.

The effects of linaclotide on intestinal motility were evaluated in pharmacodynamics studies using animal models, and a dose-dependent increase in bowel transit was demonstrated in rats (29). In addition, from the exposure of ligated small bowel loops to linaclotide a significant increase in fluid secretion was deduced, which was associated with an also significant increase in intraluminal GMPc levels (29).

Given their implications for clinical development, animal studies were particularly relevant, as they showed a decrease in visceral pain. Eutamene et al. (30), using up to four different visceral hypersensitivity models in mice, concluded that linaclotide exerts a powerful anti-nociceptive effect as a result of GC-C receptor activation. This effect was only seen under colorectal distension conditions, not under basal conditions; furthermore, the effect was only obtained with low doses, which may indicate a loss of specificity for higher doses (28). These results suggest that GC-C also plays a role in the modulation of sensitive responses to distension only in the presence of hypersensitivity. These findings are in contrast with others derived from experiments in mice genetically conditioned not to express the GC-C gene, which suggest that GC-C receptor activation is associated with sensitivity under basal conditions but not in the presence of hypersensitivity (28). Subsequent *in vitro* studies with different linaclotide doses have explored responses under both basal and hypersensitivity conditions, both to high- and low-threshold nociceptive stimuli (31). A possibility stemming from all these results is that GC-C activation may play a role both under hypersensitivity conditions and in case of low-threshold mechanical sensitivity under basal conditions. A very interesting use of linaclotide may be extrapolated from this explanation, namely an improved coordination of defecation in patients with no visceral hypersensitivity, and reduced pain in those with visceral hypersensitivity (28).

## CLINICAL STUDIES SUPPORTING THE USE OF LINACLOTIDE

Linaclotide clinical studies submitted to obtain FDA and EMA approval included eleven clinical trials (CTs), three in phase I, four in phase II, and four in phase III (28,32).

During phase I an adequate tolerance and safety was acknowledged in healthy volunteers (32). Also in volunteers and in phase Ib a decrease in stool consistency and an increase in stool weight, consistent with the expected

effect on intestinal secretion, were confirmed using ascending oral doses (32). Another phase Ib study revealed this effect to be dose-dependent (28,32,33).

During phase II a pilot randomized, double-blind, placebo-controlled clinical trial (CT) to assess the safety and tolerability, and to explore efficacy was first carried out, which found a dose-dependent response with an increase in stool frequency and a decrease in fecal consistency, with also a clinical improvement of abdominal discomfort, constipation severity, and overall symptom relief (34). A second CT was a multicenter double-blind, placebo-controlled study. All linaclotide doses improved the weekly rate of spontaneous bowel movements, which was the primary outcome; furthermore, linaclotide significantly improved the weekly rate of complete stools, fecal consistency, expulsion difficulties, abdominal discomfort, bloating, and overall symptom assessment as well as quality of life. The most common adverse event was diarrhea, but only six patients discontinued therapy because of this (35). Benefits were obtained for all variables with doses of 150 µg or higher, whereas the highest prevalence of diarrhea and the lowest effect on abdominal discomfort and bloating occurred with doses of 600 µg. This absence of dose-response effect for symptoms derived from perceived visceral pain is consistent with the results obtained from animal research.

The first phase II study in IBS-C was a phase IIa randomized, double-blind, placebo-controlled CT to assess gastrointestinal transit using scintigraphy. It was performed in 36 females with daily linaclotide doses of 100 and 1,000 µg. With 1,000 µg, but not with 100 µg, a significant decrease in mean right-colon voiding time and an increase in colonic transit were seen at 48 but not 24 hours. Similarly, significant effects of increased frequency and ease of stool passage, shortened time to first evacuation, and diminished fecal consistency were observed, all this with no identified adverse effects (36).

Second came a multicenter, double-blind, placebo-controlled CT with linaclotide doses ranging from 75 to 600 µg. A total of 420 patients, most of them females, with IBS-C according to Rome II criteria were included, who were randomized to receive placebo or linaclotide in doses of 75, 150, 300, or 600 µg for 12 weeks. Endpoints included defecation frequency, abdominal symptoms, and overall symptom assessment. The primary outcome was spontaneous complete bowel movements. A significant improvement in bowel habits was seen with all linaclotide doses, including frequency, complete stools, easy bowel movements, and fecal consistency. Abdominal pain also decreased significantly *versus* placebo. Maximum treatment effects were seen with 300 µg. Efficacy for pain symptoms, abdominal discomfort or swelling was not higher with 600 µg. Patients reporting severe pain (4-5 of 5) at least half of days at baseline experienced the greatest decrease in abdominal pain while on treatment. Over one third (37%) of patients on linaclotide experienced a clini-

cally significant improvement of IBS-QOL ( $\geq 14$  points). Treatment effects were seen as soon as in the first week and persisted for the 12 weeks' duration of the CT. Diarrhea, mild or moderate, was the only adverse event with a difference from placebo, and also was dose-dependent. Only 4% of patients had to discontinue therapy on these grounds (37).

Considering phase II results, the 150 and 300  $\mu\text{g}$  doses were selected for phase III, albeit adjusted to 145 and 290  $\mu\text{g}$  upon improved measurements of linaclotide amounts in capsules (38).

During phase III two multicenter, randomized, double-blind, placebo-controlled CTs were performed in patients with constipation and then jointly reported (39). A total of 1,272 patients were included. The primary efficacy outcome was reached by 21.2% and 16.0% of patients receiving 145  $\mu\text{g}$  of linaclotide, and by 19.4% and 21.3% of patients with 290  $\mu\text{g}$  of linaclotide, in comparison with 3.3% and 6.0% of those receiving placebo ( $p < 0.01$ ). A therapeutic effect was seen from the first day on treatment, which remained stable for the duration of therapy. The incidence of adverse events was across study groups except for diarrhea, which prompted treatment discontinuation in 4.2% of cases.

Linaclotide at 290  $\mu\text{g}$  PO daily has been tried in phase III studies, specifically in patients with IBS-C, in two additional multicenter, randomized, double-blind, placebo-controlled CTs (40,41). In one study (study 31) treatment duration was 12 weeks (40), whereas it lasted 26 weeks in the other study (study 302) (41). In their design, up to four primary efficacy endpoints were considered, taking the recommendations of both the U.S. Food and Drug Administration (FDA) and EMA (42,43) into account. Hence, the separate reports of these two trials (40,41) were then followed by a third report wherein the results of both CTs were jointly provided under the scope of the European efficacy analysis (44).

In study 31 (40), an additional 4-week period was established for randomized discontinuation. Primary and secondary outcome variables considered in this study

may be looked up in table II. This CT included a total of 800 patients (89.5% females). Its results show significant differences *versus* placebo for all primary response variables (Table III). The composite primary outcome (FDA) was reached by 33.6% of patients treated with linaclotide *versus* 21.0% of those on placebo (NNT = 8); when components were split, 48.6% *versus* 29.6% (NNT = 5.3) exhibited at least one additional spontaneous complete movement from baseline, and 50.1% *versus* 37.5% achieved at least 30% pain relief (NNT = 7.9). Significant differences were also observed in all secondary variables. Therapy response started within the first week on treatment, and reached immediately its peak for bowel

**Table II. Efficacy outcomes considered in the 12-week clinical trial of linaclotide *versus* placebo in patients with irritable bowel syndrome and constipation (study 31) (taken from reference no. 40)**

*Primary variables*

- FDA primary endpoint whereby responder is defined as subject who weekly shows an improvement of at least 30% from baseline in abdominal pain daily scores, and at least one more spontaneous complete stool in the same week for at least 6 of 12 weeks on treatment
- Abdominal pain improvement of at least 30% in at least 9 of 12 weeks on treatment
- Three or more spontaneous complete stools weekly and at least one more than at baseline also for at least 9 of 12 weeks on treatment
- A combination of criteria 2 and 3 in the same week

*Secondary variables*

- Abdominal discomfort
- Swelling
- Difficult voiding
- Stool frequency
- Fecal consistency

**Table III. Intent-to-treat results for the primary efficacy endpoints in the 12-week clinical trial of linaclotide *versus* placebo in patients with IBS-C (study 31) (taken from reference no. 40)**

Outcome variables	Response to placebo (n = 395), n (%)	Response to linaclotide (n = 405), n (%)	Risk difference (%)	p	NNT
FDA primary endpoint <sup>a</sup>	83 (21,0)	136 (33,6)	12,6	< 0,0001	8,0
Abdominal pain improvement <sup>b</sup>	107 (27,1)	139 (34,3)	7,2	0,0262	13,8
Spontaneous stools <sup>c</sup>	25 (6,3)	79 (19,5)	13,2	< 0,0001	7,6
Combined pain and stools <sup>d</sup>	20 (5,1)	49 (12,1)	7,0	0.0004	14,2

NNT: Number of patients needed to treat. <sup>a</sup>A responder is defined as a subject who weekly shows an improvement from baseline of at least 30% in the daily abdominal pain scale and at least one more spontaneous complete stool passage that same week for at least 6 of 12 weeks on treatment. <sup>b</sup>Abdominal pain improvement of at least 30% in at least 9 of 12 weeks on treatment. <sup>c</sup>Three or more spontaneous complete bowel movements weekly and at least one more versus baseline, also in at least 9 of 12 weeks on treatment. <sup>d</sup>Criteria b and c combined in the same week.

function; pain was significantly improved also within one week, but maximal relief was seen from week 6 on. During the randomized discontinuation period, patients on linaclotide maintained or developed improvement, and those who were crossed to placebo had recurring symptoms, also here with no worsening from baseline or rebound effects. No serious adverse effects occurred. Diarrhea was reported for 19.5% of subjects on linaclotide *versus* 3.5% of the placebo group, but only 5.7% of involved patients had to discontinue treatment.

In turn, study 302 (41) included 804 patients, 90% of which were females, and showed a consistent trend regarding the profiles of eligible patients. The goal also was to assess the efficacy and safety of linaclotide for IBS-C, but now for an extended period of 26 weeks. The same primary and secondary outcome variables of study 31 were considered in study 302 (Table II), and were assessed in the first 12 weeks on treatment. An additional assessment of these primary and secondary endpoints was also undertaken at 26 weeks. Other measurements were considered both at 12 and 26 weeks, including abdominal fullness, colic pain, IBS symptom severity, constipation severity, adequate IBS-C symptom relief, and level of satisfaction with IBS symptom relief and therapy overall.

The results of this second phase III CT were also conclusive regarding linaclotide effectiveness for all endpoints, whether primary or secondary, both at 12 and 26 weeks. Table IV lists these results regarding primary efficacy endpoints. In this case, the composite primary efficacy endpoint

recommended by the FDA was reached at 12 weeks by 33.7% of patients on linaclotide *versus* 13.9% of the placebo group (NNT = 5.1), whereas its components were reached by 47.6% *versus* 22.6% (NNT = 4) regarding one more spontaneous complete passage, and by 48.9% *versus* 34.5% (NNT = 6.9) for at least a pain reduction of 30%. As with study 31, therapy response began within one week on treatment, and was maximal from the start for bowel function, while the maximal effect on pain was seen at week 8. Differences *versus* placebo were maintained through week 26. At therapy end 45% of patients on linaclotide said they were very or quite satisfied with their treatment, *versus* 20% of patients on placebo. Furthermore, 56% *versus* 33% reported an adequate relief of IBS-related symptoms; this proportion rose to 72% *versus* 45% when any relief was considered. The rate of adverse events was similar across treatment arms except for diarrhea (19.7% *versus* 2.5%), which only led to discontinuation in 4.5% of patients in the linaclotide group *versus* 0.2% of those in the placebo group, with no consideration of serious adverse event for any subjects.

A third report (44) has already been mentioned, which provides a joint analysis of both previous CTs from the perspective of the primary endpoints suggested by the EMA (Table V). Bearing in mind these primary variables, the result obtained for efficacy regarding pain relief was 58.4% in the linaclotide arm *versus* 41.8% in the placebo arm in study 31, and 54.1% *versus* 38.5% in study 302 ( $p < 0.001$  in both cases). As regards symptom relief, 37.0% of subjects on linaclotide *versus* 18.5% of subjects in the control group responded in study 31, in comparison with 39.4%

**Table IV. Intent-to-treat results for the primary efficacy endpoints in the 26-week CT of linaclotide *versus* placebo in subjects with IBS-C (study 302) (taken from reference no. 41)**

Results at 12 weeks				
Outcome variables	Response to placebo (n = 403)%	Response to linaclotide (n = 401)%	Risk difference (%)	NNT (95% CI)
FDA primary endpoint <sup>a</sup>	13,9	33,7	19,8	5,1 (3,9; 7,1)
Abdominal pain improvement <sup>b</sup>	19,6	38,9	19,3	5,2 (3,9; 7,6)
Spontaneous stools <sup>c</sup>	5,0	18,0	13,0	7,7 (5,8; 11,5)
Combined pain and stools <sup>d</sup>	3,0	12,7	9,7	10,3 (7,5; 16,4)
Results at 26 weeks				
Outcome variables	Response to placebo (n = 403)%	Response to linaclotide (n = 401)%	Risk difference (%)	NNT (95% CI)
FDA primary endpoint <sup>a</sup>	13,2	32,4	19,2	5,2 (4,0; 7,3)
Abdominal pain improvement <sup>b</sup>	17,4	36,9	19,5	5,1 (3,9; 7,4)
Spontaneous stools <sup>c</sup>	3,5	15,7	12,2	8,2 (6,2; 12,1)
Combined pain and stools <sup>d</sup>	2,5	12,0	9,5	10,5 (7,7; 16,8)

NNT: Number of patients needed to treat. <sup>a</sup>A responder is defined as a subject who weekly shows an improvement from baseline of at least 30% in the daily abdominal pain scale and at least one more spontaneous complete bowel movement in the same week for at least 6 of 12 weeks on treatment. <sup>b</sup>Abdominal pain improvement of at least 30% in at least 9 of 12 weeks on treatment. <sup>c</sup>Three or more spontaneous complete bowel movements weekly and at least one more versus baseline also in at least 9 of 12 weeks on treatment. <sup>d</sup>Criteria b and c combined in the same week.

versus 16.6% in study 302 ( $p < 0.0001$  in both cases). Additionally, in study 302, a significantly greater number of patients on linaclotide responded beyond week 13 as compared to placebo: 53.6% for pain or discomfort versus 36.0%; 37.2% versus 16.9% for symptom relief ( $p < 0.0001$  in both cases). The percentage of sustained responses (proportion of responders who maintained their response for at least two of the last four weeks on treatment) was also significantly higher in the linaclotide arm in both studies ( $p < 0.001$ ).

## VALIDITY AND CLINICAL APPLICABILITY OF RESULTS

Regarding safety, a very low drug bioavailability was relevant in the preclinical development phase, which suggested systemic toxicity was unlikely. The results of trials in humans confirmed the virtually absent presence of linaclotide in the blood after oral dosing. This is consistent with the fact that no significant differences in adverse effects was noted between the placebo arm and the experimental arm in clinical-phase CTs, except for those derived from the drug's effect itself, as is the case with diarrhea. That is, no toxicity from systemic exposure could be attributed to linaclotide.

Diarrhea, the adverse effect most commonly reported, may somehow be considered an excessive therapeutic action linked to the drug's mechanism of action rather than an undesired, unexpected consequence. From a clinical perspective, the fact that a previously constipated patient goes on to report diarrhea should be examined on an individual basis with a dual focus: The objective and perceived severity of diarrhea, and its tolerability by patients. Linaclotide CTs have shown that no case of diarrhea was a severe adverse event; moreover, it did not even warrant discontinuation except for a small percentage of individuals. It is therefore seemingly reasonable to assume that, in clinical practice, the development of diarrhea following a dose of linaclotide may be considered a factor associated with the symptomatic course of a previous constipation episode, and may thus be easily managed, as it is not serious and usually not severe enough to lead to treatment discontinuation.

During the preclinical development of linaclotide virtually all aspects relevant for the upcoming clinical phase were satisfactorily elucidated. Some reservations apply only regarding the complete elucidation of the intimate mechanism behind the dual, positive effect of linaclotide, which not only increases intestinal secretion but also decreases visceral pain. Conceptually, this is a relevant topic with respect to basic objective knowledge, but not so much regarding the propriety of clinical development as based on the dual therapeutic goal of both constipation and pain relief. During the preclinical phase, events followed a logical sequence: Molecule identification, secretory effect acknowledgment, painkiller effect observed as an additional finding, and preclinical redefinition of therapy targets. The fact that the explanation of its analgesic effect is speculative, although well grounded and based on sound experiments, in no way harms the validity of the experimental observation itself. Therefore, it was perfectly plausible to translate the exploration of abdominal pain relief into clinical development. Clinical results have been consistent along this line to the extent that the EMA considers that linaclotide's indication is precisely IBS-C, an illness where obtaining the above dual effect is paradigmatic. Nevertheless, given that the limits between symptomatic chronic constipation and IBS-C may be blurry, the stance adopted by the FDA, which endorses both the indications of IBS-C and chronic constipation, is also sound.

As regards clinical development, we should mention methodological amendments in each and every phase, and regarding the highly consistent results in terms of effect and even effect size. Focusing on phase III, all trials performed meet every usually stringent requirement in terms of patient screening, randomization into the experimental and placebo arms, blinding, hidden randomization sequences, and clear definition of endpoints and outcome variables.

Regarding patient screening every effort was made to meet the mandatory diagnostic criteria so that results could be then extrapolated to the explored indication. Hence the expected reduction from eligible to randomizable subjects. This proper screening also explains the consistently high proportion of females, which only reflects the clinical profile of the conditions involved, with no different therapy effects according to gender being expected from these results or the existing data.

**Table V. Co-primary endpoints pre-specified by the European Medicines Agency (EMA) and considered primary efficacy outcomes in phase III clinical trials of linaclotide versus placebo in subjects with irritable bowel syndrome and constipation (from reference no. 44)**

### Co-primary endpoints - EMA

- Response at 12 weeks defined as a reduction of at least 30% in mean weekly abdominal pain/discomfort scores, with no worsening from baseline, for at least 50% of treatment duration (6/12 weeks).
- Response at 12 weeks defined as a weekly response of considerable or complete IBS symptom relief for at least 50% of treatment duration (6/12 weeks).

Primary outcome variables were not selected because of methodological convenience in searching for a higher probability of difference but according to objective criteria recommended by regulatory agencies, which provides CTs with an added value of accordance with previously established outcome standards.

It is just this conjunction of a representative population and relevant endpoints (established regardless of sponsor or researcher-related interests) that allows a better interpretation of the sense and magnitude of the results obtained.

Results demonstrate the undoubtable efficacy of linaclotide, but their relevance should be scrutinized. Regarding IBS-C, overall and in a nutshell, approximately 50% of patients may be said to respond to treatment, and up to three fourths considered it provided relief. However, more strictly, objective differences between placebo and treatment (only for primary outcome variables, table VI) range from 12.8% to 22.8% (NNT, 8 to 4.4). We may endorse that, approximately and operationally, at least 13%—maybe up to 20%—of patients will jointly respond to pain and constipation (FDA outcomes), and consistently for EMA variables, 16% will respond with objective pain improvement, and up to 20% with symptom relief. On the other hand the effect of therapy is clearly seen from the start, and reaches peak effectiveness early for intestinal function and later for pain relief. Response sustainability and lack of symptom rebound again demonstrate—together with the aforementioned consistency in effect direction—that a specific therapy target exists in the selected population.

In summary, regarding IBS-C, most patients perceive an improvement of symptoms, but an objective complete response, measured by the primary outcome variables used by CTs *versus* placebo, is obtained in around 16-18% of subjects. Given the clinical complexity of IBS-C, and the

interaction of various mechanisms in its pathogenesis, these patients who reach an objective response will likely be those where the predominant pathophysiological mechanism is reverted by linaclotide, therefore those where this drug provides not only marginal relief but also exerts a direct, univocal therapeutic action. A logical follow-on to this approach is to endorse the propriety of linaclotide indication and use for this type of patients in clinical practice.

However, two relevant topics remain to be developed during the post-approval stage, together with the pharmacovigilance requirements, most particularly regarding the adverse event diarrhea, that the EMA demands. The first one refers to which therapy duration should be recommended for responders. We know that response is expected to be sustained for at least 26 weeks, but no follow-up data are available for the longer term. Given the benign characteristics of this disease, its potential natural history with on and off stages, the absence of rebound following discontinuation, and the drug's rapid effect, it seems reasonable to assume that the clinical use of linaclotide will likely involve discontinuation/reintroduction regimens according to symptomatic stages rather than follow a continuous, indefinite pattern of use. Anyway, this relevant matter of optimal treatment duration should be prospectively evaluated in the immediate future. The second topic is about the elucidation of differences between responders and non-responders. From completed CTs no characteristics are derived allowing to predict which patient may respond to linaclotide and which patient may not. It is precisely because linaclotide is a drug that explores a specific mechanism of action to which some patients respond and some others do not, a continuation of clinical research on this product would be highly relevant in an attempt to define the characteristics associated with non-response

**Table VI. Intent-to-treat results for primary efficacy variables (FDA and EMA) in 12-to-24 week CTs of linaclotide *versus* placebo in patients with IBS-C (studies 31 and 302, respectively) (taken from references 40, 41 and 44)**

<i>Study 31</i>		
<i>Outcome variables</i>	<i>Difference in risk (%)</i>	<i>NNT</i>
FDA, primary at 12 weeks <sup>a</sup>	12,6	8
EMA, pain at 12 weeks	16,6	6
EMA, symptom relief at 12 weeks	18,5	5,4
<i>Study 302</i>		
<i>Outcome variables</i>	<i>Difference in risk (%)</i>	<i>NNT</i>
FDA, primary at 12 weeks <sup>a</sup>	19,8	5,1
FDA, primary at 26 weeks <sup>a</sup>	19,2	5,2
EMA, pain at 12 weeks <sup>b</sup>	15,6	6,4
EMA, symptom relief at 12 weeks <sup>c</sup>	22,8	4,4

NNT: Number of patients needed to treat. <sup>a</sup>Responder defined only as a subject who weekly shows an improvement of at least 30% from baseline in the daily abdominal pain scale and at least one complete spontaneous stool passage. <sup>b</sup>Response at 12 weeks defined as at least a 30% reduction in mean weekly abdominal pain/discomfort scores, with no worsening from baseline, for at least 50% of treatment duration (6/12 weeks). <sup>c</sup>Response at 12 weeks defined as a weekly response of considerable or complete IBS symptom relief for at least 50% of treatment duration (6/12 weeks).

or response, according to the chosen focus. Having this information available beforehand would have been perfect, though waiting for wider studies or studies specifically designed with this end in mind does not seem enough to warrant the delayed incorporation of the drug into clinical practice for those patients who can benefit from it, as seemingly considered by both the EMA and FDA.

In practice, consistent with the above, an absence of response prediction rules does not obviously eliminate the need to select patients who may specifically benefit from linaclotide. In this respect, the clinical development and approval of linaclotide provides alternative clues for an acceptable roadmap. First, as a compulsory premise, only indication-related patients may be eligible, that is, patients meeting Rome III criteria for moderate to severe IBS-C. An additional, reasonable clinical interpretation leads to consider that these patients' profile corresponds to subjects failing to respond to prior routine treatments with expanders/laxatives and spasmolytics, always following the exclusion of disease-specific mechanisms for IBS, in accordance with the first part of this report. Once in a scenario involving a patient who meets IBS-C criteria, has significantly severe symptoms, and fails to adequately respond to mechanism-specific or general therapies using expanders/laxatives and spasmolytics, the appropriate thing to do is to initiate therapy with linaclotide, given its absence of significant adverse effects bar diarrhea, which really is an exacerbation of the drug's own action as discussed above. If response to therapy ensues, we know this will occur early, hence in the absence of response there is no sense in maintaining therapy beyond the initial 4-week course. Therefore, this test period may in practice represent the best approach to patient selection, always following the above-mentioned steps.

## ACKNOWLEDGMENTS

The original report on which this review is based was discussed, improved and validated by various SEPD senior members, to whom the author is grateful for their contribution.

## CONFLICTS OF INTEREST

This manuscript is an adapted-for-publication version of an internal report that was previously developed by the author as person responsible for *Comité de Excelencia Clínica* within *Sociedad Española de Patología Digestiva* (SEPD). The goal pursued by SEPD was to develop its own scientific, independent, objective view on the opportunity to introduce linaclotide in our country for the management of patients with irritable bowel syndrome and constipation (IBS-C). Both SEPD and the author have no relationship or interest of sorts regarding Ironwood

Pharmaceuticals, the initial developers of linaclotide. The author has no contractual relationship or interest regarding Almirall, S.A. Both the original report and this paper have been developed using own sources, with no contributions or direct/indirect cooperation from Ironwood Pharmaceuticals, Almirall, or any other related agent. SEPD has agreements with Almirall, S.A. exclusively for the organization of educational activities during their annual conference. Neither the report nor this manuscript were elaborated at the request of the aforementioned pharmaceutical companies. No compensations have been established, and no link or specific agreement exists with respect to linaclotide. This notwithstanding, SEPD wishes to validate this paper, hence has authorized the writing of this version.

## REFERENCES

1. CHMP summary of positive opinion for Constella. EMA/CHMP/604998/2012. 2012. [Consultado 26/02/2013]. Disponible en: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Summary\\_of\\_opinion\\_-\\_Initial\\_authorisation/human/002490/WC500132840.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002490/WC500132840.pdf).
2. Mearin F, Lacy BE. Diagnostic criteria in IBS: Useful or not? *Neurogastroenterol Motil* 2012;24:791-801.
3. Fortea J, Prior M. Irritable bowel syndrome with constipation: A European-focused systematic literature review of disease burden. *J Med Econ* 2013;16:329-41.
4. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006;130:1480-91.
5. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:712-21 e4.
6. Caballero-Plasencia AM, Sofos-Kontoyannis S, Valenzuela-Barranco M, Martín-Ruiz JL, Casado-Caballero FJ, López-Manas JG. Irritable bowel syndrome in patients with dyspepsia: A community-based study in southern Europe. *Eur J Gastroenterol Hepatol* 1999;11:517-22.
7. Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, et al. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: Comparison of Rome II versus previous criteria in a general population. *Scand J Gastroenterol* 2001;36:1155-61.
8. Rey E, Mearin F. Prevalencia de trastornos funcionales intestinales en la población española y su asociación con síntomas digestivos altos. *Rev Esp Enferm Dig* 2012;104 (Supl. I):89-90.
9. Mearin F. Without doubt, functional digestive disorders constitute one of the main reasons for consultation in both gastroenterology and primary health care. Foreword. *J Clin Gastroenterol* 2011;45 (Supl.):S81.
10. Fedorak RN, Vanner SJ, Paterson WG, Bridges RJ. Canadian Digestive Health Foundation Public Impact Series 3: Irritable bowel syndrome in Canada. Incidence, prevalence, and direct and indirect economic impact. *Can J Gastroenterol* 2012;26:252-6.
11. Mitra D, Davis KL, Baran RW. All-cause health care charges among managed care patients with constipation and comorbid irritable bowel syndrome. *Postgrad Med* 2011;123:122-32.
12. Agarwal N, Spiegel BM. The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. *Gastroenterol Clin North Am* 2011;40:11-9.
13. Rey E, García-Alonso MO, Moreno-Ortega M, Álvarez-Sánchez A, Díaz-Rubio M. Determinants of quality of life in irritable bowel syndrome. *J Clin Gastroenterol* 2008;42:1003-9.
14. Pique JM, Lanas A. Síndrome del intestino irritable: una enfermedad con una elevada carga socioeconómica y sanitaria. *Aten Primaria* 2006;38:69-71.
15. Dibonaventura MD, Prior M, Prieto P, Fortea J. Burden of constipation-predominant irritable bowel syndrome (IBS-C) in France, Italy, and the United Kingdom. *Clin Exp Gastroenterol* 2012;5:203-12.

16. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;15:355-61.
17. Clave P, Acalovschi M, Triantafyllidis JK, Uspensky YP, Kalayci C, Shee V, et al. Randomised clinical trial: Otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2011;34:432-42.
18. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. *Gut* 2009;58:367-78.
19. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984;29:239-47.
20. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol Suppl* 1987;130:81-4.
21. Efskild PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol* 1996;31:463-8.
22. Tack J, Fried M, Houghton LA, Spicak J, Fisher G. Systematic review: The efficacy of treatments for irritable bowel syndrome - a European perspective. *Aliment Pharmacol Ther* 2006;24:183-205.
23. Andresen V, Montori VM, Keller J, West CP, Layer P, Camilleri M. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol* 2008;6:545-55.
24. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2008;27:685-96.
25. Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, et al. Clinical trial: Lubiprostone in patients with constipation-associated irritable bowel syndrome - results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 2009;29:329-41.
26. Chey WD, Drossman DA, Johanson JF, Scott C, Panas RM, Ueno R. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2012;35:587-99.
27. Potter LR. Regulation and therapeutic targeting of peptide-activated receptor guanylyl cyclases. *Pharmacol Ther* 2011;130:71-82.
28. Corsetti M, Tack J. Linaclotide: A new drug for the treatment of chronic constipation and irritable bowel syndrome with constipation. *United European Gastroenterology Journal* 2013;1:7-20.
29. Busby RW, Bryant AP, Bartolini WP, Cordero EA, Hannig G, Kessler MM, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol* 2010;649:328-35.
30. Eutamene H, Bradesi S, Larauche M, Theodorou V, Beaufrand C, Ohning G, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil* 2010;22:312-e84.
31. Brierley SM. Guanylate cyclase-C receptor activation: Unexpected biology. *Curr Opin Pharmacol* 2012;12:632-40.
32. Vazquez Roque M, Camilleri M. Linaclotide, a synthetic guanylate cyclase C agonist, for the treatment of functional gastrointestinal disorders associated with constipation. *Expert Rev Gastroenterol Hepatol* 2011;5:301-10.
33. Busby RW, Kessler MM, Bartolini WP, Bryant AP, Hannig G, Higgins CS, et al. Pharmacologic properties, metabolism, and disposition of linaclotide, a novel therapeutic peptide approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. *J Pharmacol Exp Ther* 2013;344:196-206.
34. Johnston JM, Kurtz CB, Drossman DA, Lembo AJ, Jeglinski BI, MacDougall JE, et al. Pilot study on the effect of linaclotide in patients with chronic constipation. *Am J Gastroenterol* 2009;104:125-32.
35. Lembo AJ, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology* 2010;138:886-95 e1.
36. Andresen V, Camilleri M, Busciglio IA, Grudell A, Burton D, McKinzie S, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2007;133:761-8.
37. Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology* 2010;139:1877-86 e2.
38. Johnston JM, Schneier HA. Clarification of trial end points presented in a recent review of linaclotide. *Expert Rev Gastroenterol Hepatol* 2012;6:13-4.
39. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 2011;365:527-36.
40. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012;107:1714-24.
41. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: A 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107:1702-12.
42. European Medicines Agency. Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome. 2003. [Consultado 26/02/2013]. Disponible en: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003187.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003187.pdf).
43. Guidance for industry: irritable bowel syndrome - clinical evaluation of drugs for treatment. Food and Drug Administration. 2012. [Consultado 26/02/2013]. Disponible en: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf>.
44. Quigley EM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, et al. Randomised clinical trials: Linaclotide phase 3 studies in IBS-C - A prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther* 2013;37:49-61.