EXPERT REVIEWS

How can we achieve relief of bowel and abdominal symptoms for patients with irritable bowel syndrome with constipation?

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Current interventions for irritable bowel syndrome with constipation tend to target single symptoms of the disorder, with multiple symptom relief only achieved through the use of combinations of therapies. Hence, there remains an unmet need for well-tolerated and effective treatments for irritable bowel syndrome with constipation that target abdominal symptoms, including abdominal pain and bowel symptoms.

Keywords: abdominal pain • bloating • constipation • European Medicines Agency • gender • irritable bowel syndrome • linaclotide • quality of life

Patients with irritable bowel syndrome (IBS) perceive symptoms of abdominal pain, bloating, constipation and fatigue as more important than other constipation-related symptoms such as straining, incomplete evacuation and hard stool consistency [1]. The fundamental clinical significance of these symptoms is reflected by both the EMA and the US FDA guidelines for the conduct of clinical trials in IBS, which recommend the assessment of abdominal pain as a key efficacy parameter [2].

Linaclotide is a novel, first-in-class minimally absorbed guanylate cyclase C agonist recently approved by the EMA for the symptomatic treatment of moderate-to-severe IBS with constipation (IBS-C) in adults [101], and by the FDA for the treatment of IBS-C and chronic constipation in adults [102,103]. Linaclotide acts locally on guanylate cyclase C receptors expressed in the intestine to stimulate secretion of chloride and bicarbonate ions and water into the intestinal lumen, improving gastrointestinal motility [3–5]. In animal models, activation of guanylate cyclase C receptors by linaclotide also results in desensitization of the nerves responsible for pain sensation in the bowel, alleviating visceral hypersensitivity and, therefore, symptoms of pain and discomfort [6].

The potential for linaclotide as a novel therapy for IBS-C was demonstrated in early clinical trials. In Phase I studies in healthy volunteers, linaclotide was well tolerated with low oral bioavailability and a favorable safety profile [7,8]. Furthermore, linaclotide was shown to soften stool consistency and increase the frequency of bowel movements. Additional evidence of the beneficial effect of linaclotide on bowel symptoms of IBS-C was demonstrated in Phase II studies, where linaclotide accelerated colonic transit and emptying, and improved bowel function (including bowel movement frequency), stool consistency and severity of straining [9,10]. Linaclotide also significantly reduced abdominal pain severity associated with IBS-C [10]. Based on the balance of efficacy and tolerability, a dose of linaclotide 290 µg once daily was selected for Phase III evaluation. This article reviews the results of the Phase III studies, focusing on the EMA-specified end points.

Linaclotide for the treatment of IBS-C: evidence from Phase III studies

Study design

Both Study 31 and Study 302 were randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase III studies of linaclotide 290 µg [11–13]. Study 31 was a

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12-week study with an additional double-blind, 4-week randomized-withdrawal period in which patients initially randomized to linaclotide were re-randomized (1:1) to linaclotide or placebo, and patients initially randomized to placebo were assigned to linaclotide [11]. Study 302 was a 26-week study with the primary end points evaluated over the first 12 weeks of treatment [12].

In both studies, the coprimary end points prespecified by the EMA were 12-week abdominal pain or discomfort responders, and 12-week IBS degree-of-relief responders [13]; these and other EMA-related end points are described in Table 1. Analysis of these studies using end points prespecified by the FDA has been described in detail elsewhere [11,13].

Abdominal symptoms

Results from both studies showed that, in comparison with placebo, a significantly greater proportion of patients treated with linaclotide met the criteria for abdominal pain or discomfort responders at week 12 ($p < 0.0001$ for both studies) and week 26 (Study 302; $p < 0.001$) (Table 2) [13]. The threshold for abdominal pain or discomfort response was an improvement of at least 30% from baseline in mean abdominal pain or abdominal discomfort scores for at least 6 out of 12 weeks, with neither worsening from baseline for that week [13]. Results from chronic pain studies have indicated that an improvement of this magnitude in pain intensity score is considered clinically meaningful [14].

Relief of abdominal pain with linaclotide was rapid, with response observed from week 1, and linaclotide continued to provide sustained relief of abdominal pain or discomfort for the duration of each study, with significantly more patients meeting criteria for a sustained abdominal pain or discomfort responder at week 12 (Study 31: $p < 0.001$; Study 302: $p < 0.0001$) and week 26 (Study 302: $p < 0.0001$), versus placebo (Table 2) [13].

Furthermore, linaclotide showed significant improvements versus placebo in both studies for all secondary abdominal end points at week 12, including: abdominal pain ($p < 0.0001$ for both studies), abdominal pain-free days (Study 31: $p < 0.01$; Study 302: $p = 0.0003$) and abdominal discomfort ($p < 0.0001$ for both studies) (Table 2) [13]. Data from Study 302 showed that at all time points over the 26-week study, linaclotide significantly improved relative change in worst abdominal pain and abdominal pain or discomfort versus placebo ($p < 0.001$ and $p < 0.0001$, respectively) [12,13].

Further evidence of the clinical effectiveness of linaclotide against symptoms of abdominal pain was observed in patients who were re-randomized to remain on linaclotide during the 4-week randomized-withdrawal period of Study 31 [11,13]. These patients experienced continued relief of abdominal pain, showing durability of response, whereas those patients re-randomized from linaclotide to placebo experienced a gradual worsening of abdominal pain symptoms to levels experienced by patients originally randomized to placebo. However, there was no indication of a 'rebound' or worsening of symptoms relative to baseline in these patients. Patients who were assigned from placebo to linaclotide showed levels of improvement similar to those experienced by linaclotide patients during the treatment period.

Post-hoc analyses of these Phase III data suggested that relief of abdominal pain symptoms with linaclotide was independent of severity of pain prior to treatment [15] and that the relief of abdominal pain associated with linaclotide was predominantly a direct effect (~90%) rather than mediated through improvements in complete spontaneous bowel movement (CSBM) frequency (~10%) [16].

Table 1. Linaclotide Phase III studies: EMA-specified end points.

EMA-required end point	Definition
Coprimary end points	
12-week abdominal pain/discomfort responder	A patient who, for at least 6 out of 12 weeks, has an improvement of ≥30% in mean abdominal pain or abdominal discomfort scores for that week with neither score worsening from baseline for that week
12-week IBS degree-of-relief responder	A patient who, for at least 6 out of 12 weeks, reports degree-of-relief of IBS symptoms (i.e., 'considerably' or 'completely' relieved)
Additional end points	
Abdominal pain or discomfort sustained responder	A 12-week (Study 31 and Study 302) or 26-week (Study 302 only) abdominal pain or discomfort responder who was also a responder for ≥2 of the last 4 weeks of the patients' treatment
IBS degree-of-relief sustained responder	A 12-week (Study 31 and Study 302) or 26-week (Study 302 only) IBS degree-of-relief responder who was also a responder for ≥2 of the last 4 weeks of the patients' treatment
Secondary end points	26-week abdominal pain or discomfort responder, 26-week IBS degree-of-relief responder, CSBM frequency, SBM frequency, stool consistency, bloating, severity of straining and quality of life

†The studies were also analyzed according to US FDA-required end points.
CSBM: Complete spontaneous bowel movement; IBS: Irritable bowel syndrome; SBM: Spontaneous bowel movement.
Based on [13].

Table 2. Primary and secondary end points in Study 31 and Study 302.

End points	Study 31		Study 302	
	Placebo (n = 395)	*Linaclotide (n = 405)*	*Placebo (n = 403)*	*Linaclotide (n = 401)*
EMA-required coprimary end points				
12-week abdominal pain or discomfort responders (%)	41.8	54.8**	38.5	54.1***
12-week IBS degree-of-relief responders (%)	18.5	37.0***	16.6	39.4***
Additional EMA-required end points				
12-week abdominal pain or discomfort sustained responder (%)	41.5	53.1**	38.0	53.6***
26-week abdominal pain or discomfort sustained responder (%)			33.3	51.9***
12-week IBS degree-of-relief sustained responder (%)	18.2	33.8***	15.6	36.7***
26-week IBS degree-of-relief sustained responder (%)			14.1	33.2***
12-week secondary end points, change from baseline				
CSBM frequency per week†	0.7	2.3***	0.7	2.2***
Stool consistency (BSFS scale)†‡	0.7	2.1***	0.6	1.9***
Severity of straining (five-point ordinal scale)†‡	-0.7	-1.3***	-0.7	-1.2***
Bloating (11-point NRS scale)†	-1.1	-1.9***	-1.0	-1.9***
SBM frequency per week	1.1	3.9***	1.3	4.0***
Abdominal pain (11-point NRS scale)	-1.1	-1.9***	-1.1	-1.9***
Abdominal pain-free days (%)	5.3	9.8*	4.8	10.5**
Abdominal discomfort (11-point NRS scale)	-1.2	-2.0***	-1.1	-1.9***
12-week health outcome end points, change from baseline				
IBS-QoL overall score§	15.0	18.5*	11.0	17.3***
EuroQoL 5D utility index score§	0.05	0.08*	0.05	0.09**
EuroQoL 5D visual analog scale§	3.9	6.3	4.7	7.0*

*p < 0.01 vs placebo; **p < 0.001 vs placebo; ***p < 0.0001 vs placebo. P-values were based on the comparison of linaclotide vs placebo using the analysis of covariance model.
†Statistical significance based on nominal p-values and the methodology used to control for multiplicity.
‡n = number of patients in the ITT population with analysis values at baseline and during the treatment period.
§n = patients in the ITT population who had both baseline and ≥1 postrandomization health outcome assessment entry for IBS-QoL or EQ 5D.
BSFS: Bristol Stool Form Scale; CSBM: Complete spontaneous bowel movement; IBS: Irritable bowel syndrome; ITT: Intent-to-treat; NRS: Numeric rating scale; QoL: Quality of Life; SBM: Spontaneous bowel movement.
Data taken from [11–13].

Bowel symptoms

In addition to relieving abdominal symptoms, linaclotide also provides relief of bowel symptoms. Results from both Phase III studies showed that, in comparison with placebo, a significantly greater proportion of patients treated with linaclotide met the criteria for IBS degree-of-relief responders at week 12 ($p < 0.0001$ for both studies) and at week 26 (Study 302 only: $p < 0.001$) (Table 2) [13]. Linaclotide continued to provide relief of bowel symptoms throughout both studies, with significantly more patients meeting criteria for a sustained IBS degree-of-relief responder at week 12 (both studies) and week 26 (Study 302), versus placebo ($p < 0.001$ for all) [13].

Significant improvements were also observed for linaclotide versus placebo in both studies for all secondary bowel end points at week 12, including: CSBM frequency rate; stool consistency; severity of straining; bloating; and spontaneous bowel movement frequency ($p < 0.0001$ for all end points in both studies) (Table 2) [13]. Moreover, data from Study 302 showed that linaclotide significantly improved bloating and spontaneous bowel movement frequency versus placebo at all time points over the 26-week study period, indicating that the beneficial effects of linaclotide can be felt from week 1 of treatment and throughout the duration of administration [12,13].

Post-hoc analyses of Study 302 data suggested that patients taking linaclotide were more likely to report adequate relief and improvement in IBS symptom severity, and degree-of-relief of IBS symptoms after 26 weeks of treatment, versus placebo [17]. Furthermore, adequate relief of IBS symptoms correlated with improvements in abdominal pain and CSBM frequency.

Effect of gender

A higher prevalence of IBS has been reported in women [18] and this was reflected in the pooled male (n = 70) and female (n = 735) populations from Studies 31 and 302. When the pooled data for

the coprimary end points were stratified by gender, the difference between linaclotide and placebo was significant in both males and females for 12-week IBS degree-of-relief responder (odds ratio [OR]: 2.26 and 3.00, respectively; $p < 0.05$ for both). Differences between linaclotide and placebo for 12-week abdominal pain or discomfort responders were significant in females (OR: 1.83; $p < 0.05$). While not statistically significant, there was a trend showing that a greater proportion of males in the linaclotide versus placebo groups were responders (44.3 vs 36.0%; OR: 1.41).

When pooled data for the main secondary end points (12-week CSBM frequency rate, stool consistency, severity of straining and bloating) were stratified by gender, linaclotide provided significant improvements versus placebo across all end points in both males and females ($p < 0.05$ for all) (Figure 1), further suggesting an effectiveness of linaclotide for relieving abdominal and bowel symptoms of IBS-C in both sexes. Moreover, a consistent positive effect for linaclotide versus placebo was also observed across both female and male subgroups for all health outcome assessments.

Health outcome assessments

IBS-C can have a significant impact on quality of life and is associated with reduced work productivity and increased levels of healthcare

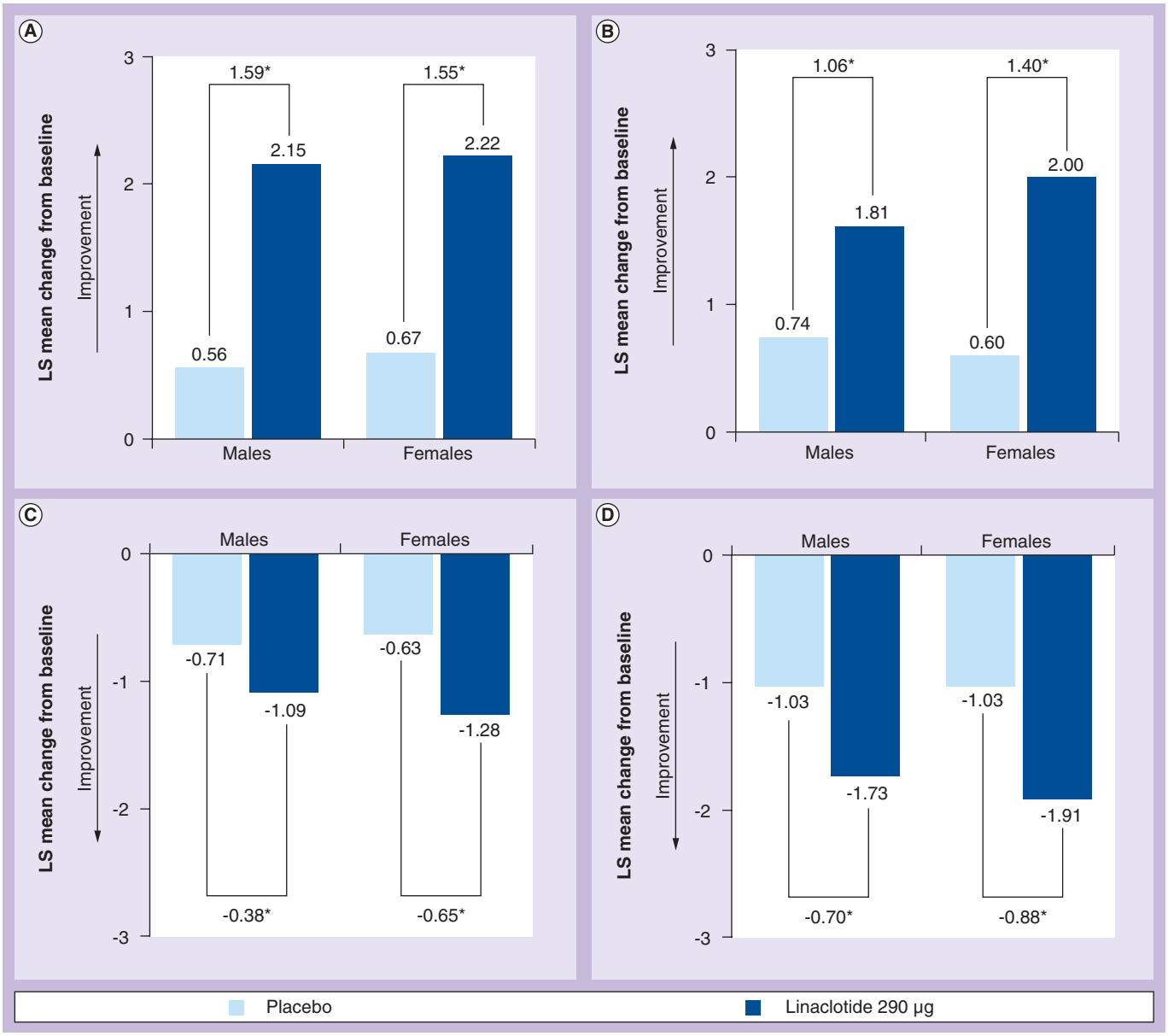

Figure 1. Subgroup analyses by gender at week 12: main secondary end points, pooled data (Study 31, Study 302). Placebo (n = 89 males and 708 females); linaclotide (n = 89 males and 735 females). **(A)** Complete spontaneous bowel movement per week, **(B)** stool consistency, **(C)** straining and **(D)** bloating.
*$p < 0.05$; intent-to-treat population.
LS: Least squares.
Based on [101].

resource utilization, both of which can result in a substantial economic burden of care [18–22]. Results from both studies indicate that linaclotide significantly improves health outcomes for patients with IBS-C, as assessed by Irritable Bowel Syndrome Quality of Life Questionnaire overall score, EuroQoL 5D utility index and EuroQoL 5D visual analog scale (Table 2) [13]. The improvements in quality of life observed with linaclotide versus placebo further support the clinical relevance of effectively treating multiple symptoms of IBS-C, including abdominal and bowel symptoms.

Post-hoc analyses of the Phase III data have provided further insight into the relationship between management of IBS-C and quality of life, indicating that linaclotide significantly improves treatment satisfaction across demographic and clinical characteristic subgroups, with the strongest correlations observed between treatment satisfaction and baseline abdominal symptoms, rather than bowel symptoms [23]. Furthermore, although baseline anxiety and depression were prevalent in the combined study population (48 and 16%, respectively), these comorbidities did not significantly impact on the symptom relief provided by linaclotide [24].

Clinical safety

Overall, a similar incidence of adverse events (AEs) was reported in the linaclotide and placebo groups (56 and 53%, respectively, in Study 31; and 65 and 57%, respectively, in Study 302) [11,12]. Serious AEs were reported by fewer than 2% of patients in either treatment group of both studies.

The most commonly reported treatment-emergent AEs were diarrhea, nausea, abdominal pain, upper respiratory tract infection, flatulence and headache. Diarrhea was reported by approximately 20% of patients versus 3% in the placebo group [13]. Diarrhea as a side effect of linaclotide was perhaps not unexpected, given that linaclotide increases fluid secretion in the gut and accelerates intestinal transit [3–5]. Importantly, the severity of diarrhea was generally mild (43%) to moderate (47%), with 2% of linaclotide-treated patients experiencing severe diarrhea [103]. Linaclotide was well tolerated, as evidenced by the relatively low incidence of diarrhea-associated discontinuations (4.5–5.7% with linaclotide vs <1.0% with placebo) [11–13]. Approximately half the diarrhea episodes started within the first week of treatment, with duration of more than 28 days reported in 21% of patients and approximately a third of diarrhea cases resolving within 7 days [103]. There were no reported serious AEs related to diarrhea [13].

Conclusion

Linaclotide is a novel treatment for IBS-C that appears to offer statistically significant and clinically relevant improvements across multiple, rather than single, symptoms of this disorder. In particular, linaclotide has demonstrated fast-acting and sustained relief of both abdominal and bowel symptoms of IBS-C for up to 26 weeks. The results from Study 31 and Study 302 confirm that regardless of whether end points were defined using FDA or EMA guidelines [11–13], linaclotide showed consistent improvements versus placebo across measures of both abdominal and bowel symptoms.

Linaclotide also improved health outcome measures in recent Phase III trials, suggesting that effective treatment of multiple symptoms of IBS-C can have a direct effect on patients' quality of life. In addition, linaclotide appeared to be well tolerated in patients with IBS-C.

In light of the clinical evidence from Phase III trials, and recent approvals by the EMA and FDA for the symptomatic treatment of moderate-to-severe IBS-C in adults in Europe [101], and for the treatment of IBS-C and chronic constipation in adults in the USA [102], linaclotide provides a new treatment option for consideration in the pharmacological management of patients with IBS-C.

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