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Review article: linaclotide for the management of irritable bowel syndrome with constipation

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SUMMARY

Background
Irritable bowel syndrome with constipation (IBS-C) represents a significant burden to patients and healthcare systems due to its prevalence and lack of successful symptomatic resolution with established treatment options. Linaclotide 290 μg has recently been approved by the European Medicines Agency (EMA) for moderate-to-severe IBS-C and by the US Food and Drug Administration for IBS-C (290 μg dose) and for chronic constipation (145 μg dose).

Aim
To summarise data leading to the approval of linaclotide for IBS-C, with focus on EMA-pre-specified outcome measures.

Methods
Literature search of a peer-review database (PubMed) and review of congress abstracts on linaclotide preclinical and clinical trial data in IBS-C.

Results
Preclinical studies suggest that the guanylate cyclase C agonist (GCCA) linaclotide acts through elevation of cyclic guanosine monophosphate (cGMP) levels, leading to accelerated gastrointestinal (GI) transit through increased fluid secretion and reduced visceral hypersensitivity. Clinical trial data demonstrate that linaclotide improves abdominal symptoms (pain, bloating) and bowel symptoms (constipation) compared with placebo in patients with IBS-C. The most frequent side effect, diarrhoea, results from the therapeutic action of linaclotide. Linaclotide acts locally in the GI tract with minimal systemic exposure, resulting in low oral bioavailability and thus a low risk of relevant systemic adverse effects.

Conclusion
Linaclotide, a first-in-class GCCA, is a promising new drug with a novel, dual mechanism of action that, unlike more well-established agents, can relieve the abdominal pain, bloating and constipation associated with IBS-C and has a low propensity for systemic side effects.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal (GI) disorder that is characterised by abdominal pain and/or discomfort, altered bowel function and a recurrence of symptoms over an extended period of time.[1]

In Europe, the estimated overall prevalence of IBS is 11.5%, ranging from 6.2% to 12.0% between countries depending on the definition applied.[2] Overall, IBS is more common in people under 50 years of age compared with older people and more common in women than men.[2–5] However, gender distribution may vary geographically and recent data suggest that while in Europe and North America IBS has a higher prevalence in women than in men, in Africa, southern Asia and South America, the prevalence of IBS may be similar in both genders.[3]

Although IBS is a benign disorder, the human cost to patients and society is vast. IBS may significantly diminish quality of life (QoL) by impairing sleep, mood, diet, intimacy and leisure activities.[1, 6] Indeed, the extent to which IBS affects health-related QoL is similar to other chronic diseases such as asthma and migraine.[7] Moreover, IBS presents a considerable societal burden in terms of the healthcare costs associated with the management of symptoms and the time lost at work,[8] not only due to its high prevalence and chronic course but also due to a substantial lack of effective treatment options.

THE NEED FOR NEW AND EFFECTIVE TREATMENTS FOR IBS WITH CONSTIPATION

Irritable bowel syndrome has a complex underlying pathophysiology that is not yet fully understood. Drugs that modify the natural history of the condition are not currently available. Treatment focuses on symptom relief and management strategies for IBS follow a 'trial and error' approach, which can be frustrating for patients and their physicians. Indeed, a survey among patients with IBS found that 40% of patients were not at all satisfied with any of the types of available medications and remedies for IBS and that 20% were not at all satisfied with the physician care they had received for IBS in the last year.[9, 10] These rates of dissatisfaction with treatments appear to be higher than those for many other chronic diseases such as migraine,[11] depression[12] or chronic constipation.[13, 14]

Altered bowel function, a hallmark feature of IBS, may present as constipation (IBS-C, irritable bowel syndrome with constipation) or diarrhoea (IBS-D), or patients may have mixed IBS (IBS-M).[15] Around one third of patients with IBS have the constipation dominant subtype, IBS-C.[2, 4, 5, 16, 17] Compared with men with IBS, women with IBS are more likely to be affected by the IBS-C subtype and less likely to have the IBS-D subtype.[3]

Most existing pharmacological treatment options for IBS-C have not been consistently studied in randomised clinical trials conducted in patients with IBS-C. They vary in their mode of action, efficacy and adverse-event profile and include fibre or bulking agents, laxatives, antispasmodics, antidepressants and lubiprostone.[18–24]

An increase in fibre intake to regulate defecation is often recommended to ease constipation. However, fibre does not improve abdominal pain symptoms in patients with IBS-C[25, 26] and, moreover, may cause bloating and abdominal distension.[27, 28] Osmotic laxatives, such as polyethylene glycol, are often prescribed for patients with IBS-C, but long-term data on the safety and efficacy of osmotic laxatives in treating IBS-C are very limited.[29, 30] Laxatives may cause side effects that are similar to the symptoms of IBS itself, including bloating and abdominal pain.[20, 21, 31] Antispasmodics are widely prescribed to relieve the abdominal pain and discomfort associated with IBS-C, but in clinical trials, the efficacy of antispasmodics in relieving global IBS symptoms and IBS-associated pain has been low.[26, 31, 32] Antidepressants, including tricyclic antidepressants (TCAs) and selective serotonin-reuptake inhibitors (SSRIs), may improve the symptoms of IBS, including abdominal pain.[26, 31, 32] However, the usefulness of antidepressants in treating IBS can be limited by side effects, which may include sexual disturbances, dry mouth, headache, dizziness, drowsiness, insomnia, constipation, nausea and bloating. In the treatment of IBS-C, SSRIs, which can accelerate GI transit, may be more suitable than TCAs, which decrease transit and may worsen constipation.[24, 33] Another class of drug prescribed for IBS-C are 5-hydroxytryptamine receptor 4 (5-HT_4) agonists, such as tegaserod and prucalopride. However, tegaserod is not available due to its unfavourable cardiovascular side-effect profile and prucalopride has not been investigated in patients with IBS-C. A new treatment for constipation associated with IBS-C is the secretagogue lubiprostone. In Phase 2 and 3 clinical studies, lubiprostone improved abdominal pain and discomfort in patients with IBS-C compared with placebo. However, this trend was not significant at all time points assessed over the 3-month treatment periods of these studies.[34, 35] In addition, lubiprostone

is not approved in many countries outside the USA, including the EU.

As a pivotal shortcoming, virtually all established pharmacological treatments for IBS-C target only single symptoms and may be associated with substantial side effects that are unacceptable in view of the essentially benign nature of the disorder. Hence, new treatment options that can effectively relieve the abdominal pain and bowel symptoms associated with IBS-C and are well tolerated would represent an important step towards improving treatment outcomes for patients with IBS-C.

REVIEW OF LINACLOTIDE

Preclinical studies and the dual mechanism of action of linaclotide

Linaclotide, a 14-amino acid synthetic peptide, is a first-in-class, high-affinity guanylate cyclase C agonist (GCCA) (Figure 1) that is homologous to the paracrine peptide hormones guanylin and uroguanylin, i.e. the endogenous activators of guanylate cyclase C (GC-C).[36]

After oral administration, linaclotide binds to and activates GC-C on colonic epithelial cells[37] and may modulate the intestinal physiology in two ways (Figure 1). Firstly, GC-C activation by linaclotide leads to increased intracellular concentrations of the second messenger cyclic guanosine monophosphate (cGMP).[37] Elevated intracellular cGMP levels activate the cGMP-dependent protein kinase II (PKG-II), leading to the phosphorylation and activation of the cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel protein at the apical surface of intestinal epithelial cells.[38, 39] CFTR activation results in the secretion of chloride and bicarbonate ions and inhibition of sodium absorption, leading to increased water flow into the intestine and the acceleration of GI transit.[37–40] Secondly, linaclotide has also been shown to reduce visceral hypersensitivity in stress-induced and inflammation-induced animal models of visceral pain.[41] These effects are also thought to be mediated through the GC-C/cGMP pathway, but involve extracellular cGMP. Linaclotide induces the secretion of cGMP as demonstrated by the accumulation of cGMP in ligated intestinal loops in rat and mouse studies[37, 40] and from human intestinal cell lines *in vitro*.[42] A recent preclinical study suggests that, upon GC-C activation by linaclotide, cGMP is actively transported across the basolateral membrane of the intestinal epithelium into the submucosal space where it acts to reduce the mechanosensitivity of colonic nociceptors, in both healthy mice and a mouse model of visceral hypersensitivity.[42] These findings, while not confirmed in humans *in vivo* (due to the nature of the experiments involved), provide a potential mechanism of action for the improvements in abdominal pain or discomfort with linaclotide treatment in clinical studies in patients with IBS-C.[42]

Importantly, linaclotide does not appear to have pharmacological activity in GC-C-deficient mice, suggesting that the actions of linaclotide are selective for GC-C.[37] Moreover, similar effects on extracellular cGMP transport and visceral hypersensitivity are seen with the natural GC-C ligand uroguanylin.[43]

Linaclotide has been shown to be stable under *in vitro* conditions mimicking the gastric environment, i.e. exposure to a highly acidic pH and gastric hydrolases.[40] After oral administration, linaclotide is metabolised in the small intestine to an active metabolite, a 13-amino acid peptide that retains linaclotide's pharmacological activity.[44, 45] Subsequently, remaining linaclotide and the active metabolite follow the common digestion pathway of proteins[45]; linaclotide is quickly degraded when incubated with mouse jejunal fluid *in vitro*.[37] In humans, approximately 3–5% of active peptides are excreted in the faeces.[45]

Linaclotide and the active metabolite are rarely detectable in plasma after oral administration of therapeutic doses, suggesting that linaclotide is not absorbed into the bloodstream.[46–50] Moreover, animal studies have shown that the expression of GC-C seems to be mainly restricted to intestinal cells.[42, 43, 51] However, GC-C is also expressed in the liver during the perinatal period, and, in the adult liver, expression is up-regulated in injury and regeneration models.[52, 53] Importantly, expression of GC-C is not detectable in key sensory tissues involved in visceral hypersensitivity, supporting the hypothesis that the analgesic effects of linaclotide are mediated via secretion of cGMP from intestinal epithelial cells where GC-C expression is abundant.[42]

As a consequence of the low oral bioavailability of linaclotide combined with the restricted expression of GC-C, the pharmacological activity of linaclotide remains limited to the GI tract, resulting in a low propensity for systemic side effects.

Phase 1 clinical studies: pharmacokinetics and pharmacodynamics of linaclotide

Three placebo-controlled Phase 1 clinical studies were carried out with linaclotide in healthy volunteers to confirm the preclinical findings.[46–48]

In two dose-ranging studies (single doses of 30–3000 μg[46]* or seven daily repeat doses of 30–1000 μg[47]*), linaclotide was well tolerated across the dose ranges and showed dose-dependent GI pharmacodynamic effects, such as loosening of stools, increasing the ease of stool passage and increasing stool frequency and weight. Importantly, even exposure to either a single dose of 3000 μg (10 times the recommended daily dose) or seven repeated doses of 1000 μg (3.3 times the recommended daily dose) did not lead to quantifiable levels of linaclotide or its main metabolite in the blood.

An open-label crossover study in healthy volunteers showed that the efficacy and tolerability of linaclotide were affected by high-fat food.[54] Hence, current prescribing information recommends that linaclotide should be taken at least 30 minutes before a meal.[54]

Phase 2 clinical studies in IBS-C

Gastrointestinal transit study. In a double-blind, placebo-controlled Phase 2a study conducted to assess the effect of linaclotide on GI transit (NCT00258193), 36 women with IBS-C according to Rome II diagnostic criteria and with a slower than average GI transit were randomised to receive placebo or one of two doses of linaclotide (100 or 1000 μg)* for 5 days.[55] Compared with placebo, linaclotide treatment significantly accelerated GI transit. Moreover, both doses led to significant improvements in stool frequency and consistency.[55] Bloating, borborygmi, loose stools, urgency and flatulence were recorded more often in at least one of the linaclotide groups compared with the placebo group. However, the frequencies of all adverse events and GI adverse events were not statistically significantly different for patients who received placebo compared with patients who received linaclotide.[55]

12-week efficacy/safety study. A 12-week, Phase 2b, multicentre, placebo-controlled, dose-ranging efficacy and safety study of linaclotide (75, 150, 300 or 600 μg once a day)* was conducted in 419 male and female patients who met the Rome II diagnostic criteria for IBS-C (NCT00460811).[56] The primary efficacy endpoint of this study was the change in the number of complete spontaneous bowel movements (CSBMs) per week for the 12-week treatment period compared with a 2-week pre-treatment baseline period. All doses of linaclotide resulted in a significant increase in the mean number of CSBMs per week in the treatment period vs. placebo. In addition, the percentage of patients who were CSBM 75% responders (patients with a weekly CSBM rate ≥3 and an increase ≥1 from baseline for ≥75% of the treatment period) was significantly greater for all doses of linaclotide (except the 150 μg dose) than for placebo.

All doses of linaclotide also led to improvements of other parameters of bowel function, including the frequency of spontaneous bowel movements (SBMs), stool consistency and straining.

Importantly, patients who received linaclotide also reported significant improvements vs. placebo in abdominal pain scores throughout the treatment period (scored daily using a 5-point scale ranging from: 1 = 'none' to 5 = 'very severe'); patients with the most severe pain during the pre-treatment period demonstrated the greatest improvements. In addition, linaclotide treatment improved other abdominal symptoms of IBS-C, such as bloating and abdominal discomfort.

Treatment effects on bowel symptoms (SBM and CSBM frequency) and abdominal symptoms (pain, discomfort and bloating) with linaclotide were seen within the first week of treatment and were sustained over the 12-week treatment period.

After treatment was stopped, benefits with respect to CSBM frequency and abdominal pain scores diminished. A rebound effect, i.e. a worsening of symptoms beyond the baseline, was not seen over a 2-week post-treatment observation period.[56]

Diarrhoea was the most common and only dose-dependent adverse event in this study, reported by 1% of patients in the placebo group and by 11–18% of patients in the linaclotide dose groups. For patients who experienced diarrhoea, the median number of days from the first dose to the onset of diarrhoea was 4 days, and most cases of diarrhoea were mild to moderate in severity.[56]

In summary, the Phase 2 studies showed that linaclotide accelerated GI transit and improved abdominal and bowel symptoms in patients with IBS-C. Although all linaclotide doses tested resulted in statistically significant effects vs. placebo, the 300 and 600 μg doses were generally more effective in the 12-week study. As the 600 μg dose was associated with a higher rate of diarrhoea than the lower

*The dose-strength expression of linaclotide changed during the Phase 1–3 clinical development programme. In the Phase 1 and Phase 2 studies, the expression of dose strength was based on total peptide content, which included inactive peptide. In the Phase 3 studies, the dose-strength expression was based on the linaclotide-specific content. The dose-strength designation of 290 μg in the Phase 3 clinical trials reflects the linaclotide content and the same dose would have been described as 300 μg in the Phase 1 and 2 clinical trials, based on the total peptide content. Therefore, the change in dose-strength expression does not indicate any change to dose potency, but merely provides a more accurate indication of the linaclotide dose used.

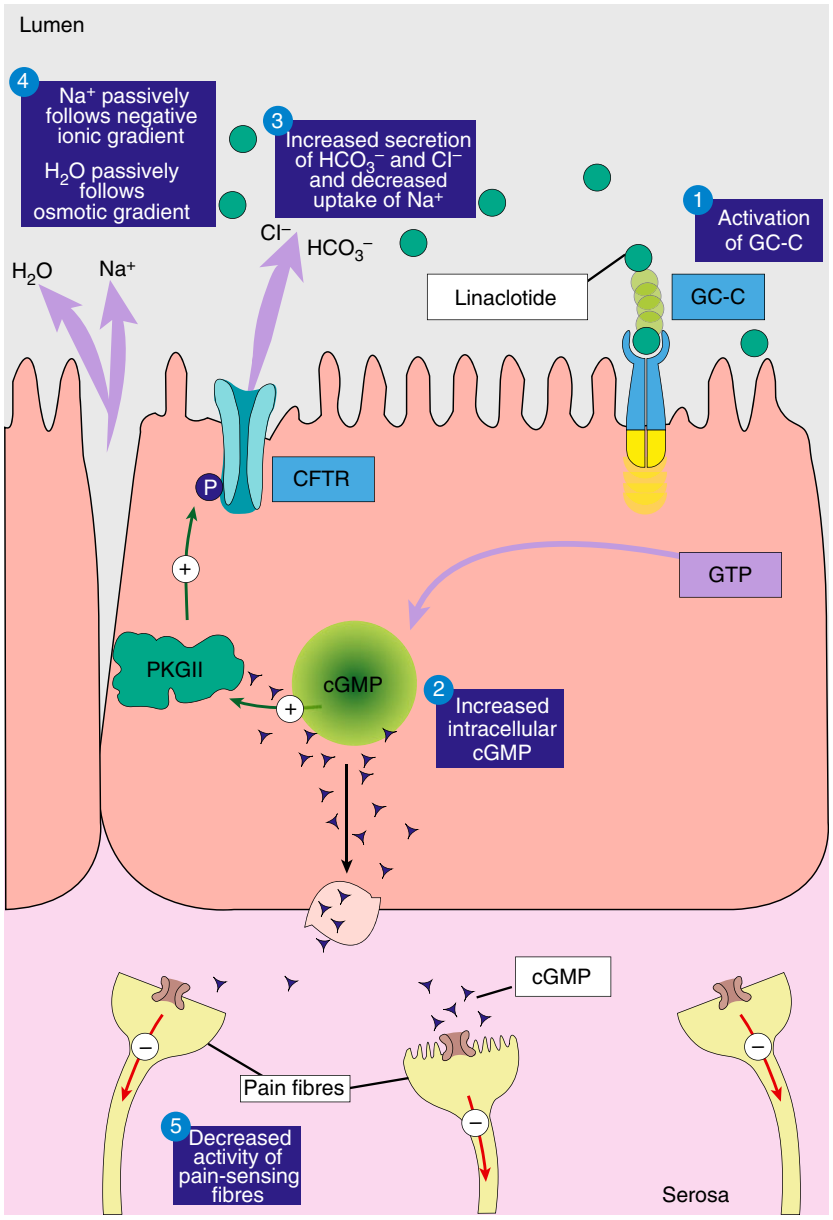

Figure 1 | Linaclotide mechanism of action.[73] cGMP, cyclic guanosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; GC-C, guanylate cyclase C; GTP, guanosine triphosphate; P, phosphorylation; PKGII, protein kinase GII. Reprinted from Blackshaw and Brierley (Emerging receptor target in the pharmacotherapy of irritable bowel syndrome with constipation. Exp Rev Gastroenterol Hepatol 2013; 7: 15-9) with permission from Expert Reviews Ltd.[73]

dose, 300 μg* was selected as the dose for further evaluation in the Phase 3 clinical trials.[56]

Phase 3 clinical studies in IBS-C: a European perspective

This review focuses on the European Medicines Agency (EMA)-specified endpoints used for the analysis in the linaclotide Phase 3 clinical trials (Table 1). The EMA recommends that the patient's global assessment of symptoms and abdominal pain/discomfort should be used as the two co-primary endpoints. Secondary efficacy endpoints should include GI symptoms such as bloating/distension, stool frequency and straining, and QoL parameters, which should be considered as the most important secondary endpoint.[57]

The US Food and Drug Administration (FDA) has issued separate guidance on the clinical evaluation for IBS treatments.[58] The four co-primary efficacy endpoints

Table 1 | European Medicines Agency-specified endpoints in linaclotide Phase 3 clinical studies[59]

Endpoint	Definition/assessment
Co-primary efficacy endpoints	
12-week abdominal pain/discomfort responder	A patient who, for ≥6 weeks out of the first 12 weeks of treatment, had an improvement of ≥30% from baseline in either mean worst abdominal pain score or mean abdominal discomfort score for that week, with neither of these scores worsening from baseline for that week
12-week IBS degree-of-relief responder	A patient whose response to the degree of relief of IBS symptoms question was 'considerably relieved' or 'completely relieved' (i.e. a score of 1 or 2) for ≥6 weeks out of the first 12 weeks of treatment
Main secondary efficacy endpoints	
26-week abdominal pain/abdominal discomfort responder	A patient who met the abdominal pain/abdominal discomfort responder definition for ≥13 weeks of 26 weeks of treatment
26-week IBS degree-of-relief responder	A patient who met the IBS degree-of-relief responder definition for ≥13 weeks of 26 weeks of treatment
12-week or 26-week sustained responder	A patient who met the responder definition and was a responder in ≥2 of the last 4 weeks of treatment
Change from baseline in 12-week CSBM frequency rate	
Change from baseline in 12-week stool consistency	Bristol Stool Formation Scale
Change from baseline in 12-week severity of straining	5-point scale ranging from: 1 = 'not at all' to 5 = 'an extreme amount'[49, 50]
Change from baseline in 12-week bloating	11-point scale ranging from: 0 = 'no bloating' to 10 = 'very severe bloating'[49, 50]
Supportive secondary parameters	
Change from baseline in 12-week SBM frequency rate	
Change from baseline in 12-week abdominal pain	11-point scale ranging from: 0 = 'no pain' to 10 = 'very severe pain'[49, 50]
Change from baseline in 12-week abdominal discomfort	11-point scale ranging from: 0 = 'no discomfort' to 10 = 'very severe discomfort'[49, 50]
Change from baseline in the EQ-5D Visual Analogue Scale score at 12 weeks	
Change from baseline in the EQ-5D Utility Index score at 12 weeks	
Change from baseline in 12-week patient assessment of IBS-QoL	

CSBM, complete spontaneous bowel movement; EQ-5D, EuroQoL-5 dimensions; IBS, irritable bowel syndrome; QoL, quality of life; SBM, spontaneous bowel movement.

for the linaclotide Phase 3 clinical trials based on the FDA guidelines have been summarised in Table 2.

Inclusion criteria. The pivotal Phase 3 clinical trial programme leading to the EMA approval of linaclotide for treating IBS-C in adults comprised two randomised, double-blind, placebo-controlled safety and efficacy studies (Study 31 and Study 302), which evaluated a total of 1604 patients with IBS-C.[49, 50, 59] The major inclusion criteria for both studies were the Rome II criteria for IBS,[15] i.e. patients had abdominal pain or discomfort for ≥12 weeks (not necessarily consecutive) in the 12 months before study entry that was characterised by at least two of the following features: (i) relieved with defecation; (ii) onset associated with a change in stool frequency; or (iii) onset associated with a change in stool form (appearance). In addition, for ≥12 weeks in the 12 months prior to study entry, eligible patients had <3 SBMs per week, experienced straining and/or lumpy or hard stools and/or a sensation of incomplete evacuation during >25% of bowel movements. In the 2-week pre-treatment period, patients eligible for randomisation reported an average daily abdominal pain score of ≥3 (on a numerical rating scale ranging from 1 to 10) and an average of <3 CSBMs and ≤5 SBMs per week.[49, 50]

Study 31: 12-week randomised treatment period followed by a 4-week randomised withdrawal period. In Study

Table 2 | US Food and Drug Administration-specified endpoints in linaclotide Phase 3 clinical studies[49, 50]

Endpoint	Definition/assessment
Co-primary efficacy endpoints	
12-week abdominal pain and CSBM (+1) responder	A patient who, for ≥6 weeks out of the first 12 weeks of treatment, had an improvement of ≥30% from baseline in mean worst abdominal pain score and an increase of ≥1 CSBM from baseline
12-week abdominal pain responder	A patient who, for ≥9 weeks out of the first 12 weeks of treatment, had an improvement of ≥30% from baseline in mean worst abdominal pain score
12-week CSBM (3 + 1) responder	A patient who, for ≥9 weeks out of the first 12 weeks of treatment, had ≥3 CSBMs and an increase of ≥1 CSBM from baseline
12-week abdominal pain and CSBM (3 + 1) responder	A patient who was a 12-week abdominal pain responder and a 12-week CSBM (3+1) responder in the same week

CSBM, complete spontaneous bowel movement.

Table 3 | Summary of linaclotide efficacy outcomes in study 31[50, 59]

	Placebo, n = 395	Linaclotide, 290 μg, n = 405	P value
Co-primary endpoints			
12-week abdominal pain/discomfort responder	41.8%	54.8%	<0.001
12-week IBS degree-of-relief responder	18.5%	37.0%	<0.0001
Additional responder analyses			
12-week sustained abdominal pain/discomfort responder	41.5%	53.1%	<0.001
12-week sustained IBS degree-of-relief responder	18.2%	33.8%	<0.0001
Change from baseline to Week 12 in:			
CSBM frequency rate	0.7	2.3	<0.0001
Stool consistency (BSFS)	0.7	2.1	<0.0001
Severity of straining	−0.7	−1.3	<0.0001
SBM frequency	1.1	3.9	<0.0001
Bloating	−1.1	−1.9	<0.0001
Abdominal pain	−1.1	−1.9	<0.0001
Abdominal discomfort	−1.2	−2.0	<0.0001
Abdominal fullness	−1.1	−2.0	<0.0001
Abdominal cramping	−1.1	−1.7	<0.0001
IBS-QoL	15.0	18.5	<0.01
EQ-5D Utility Index score	0.05	0.08	<0.01
EQ-5D Visual Analogue Scale score	3.9	6.3	NS

BSFS, Bristol Stool Formation Scale; CSBM, complete spontaneous bowel movement; EQ-5D, EuroQoL-5 dimensions; IBS, irritable bowel syndrome; NS, not significant; QoL, quality of life; SBM, spontaneous bowel movement.

31, 803 patients were randomised to either linaclotide 290 μg* or placebo for 12 weeks (NCT00948818). Most of the participants were white (77%), female (91%) and below the age of 65 years (94%, mean age 43 years). A total of 312 patients in the linaclotide group completed the initial 12-week treatment period and were re-randomised to either placebo or linaclotide 290 μg for a further 4 weeks. Patients who had initially received placebo and completed the 12-week treatment period (n = 325) were re-assigned to linaclotide 290 μg.[50]

The co-primary EMA-specified endpoints were the 12-week abdominal pain/discomfort responder rate and the 12-week IBS degree-of-relief responder rate (Table 1).[57, 59] Significantly more patients who received linaclotide were 12-week abdominal pain/discomfort responders (54.8% vs. 41.8%) and/or 12-week IBS degree-of-relief responders (37.0% vs. 18.5%) compared with patients who received placebo (Table 3). Linaclotide treatment effects were sustained over the 12-week treatment period. Hence, most patients who fulfilled the

criteria for 12-week abdominal pain/discomfort responders and/or 12-week IBS degree-of-relief responders were also sustained 12-week responders (Table 3).[59]

Linaclotide significantly improved bowel symptoms, including the frequency of CSBMs and SBMs, stool consistency and severity of straining, as well as abdominal symptoms such as bloating, pain and discomfort (Figure 2; Table 3). Analysis of the four co-primary outcomes based on the FDA guidelines also demonstrated significant improvements with linaclotide vs. placebo (Table 4).[50]

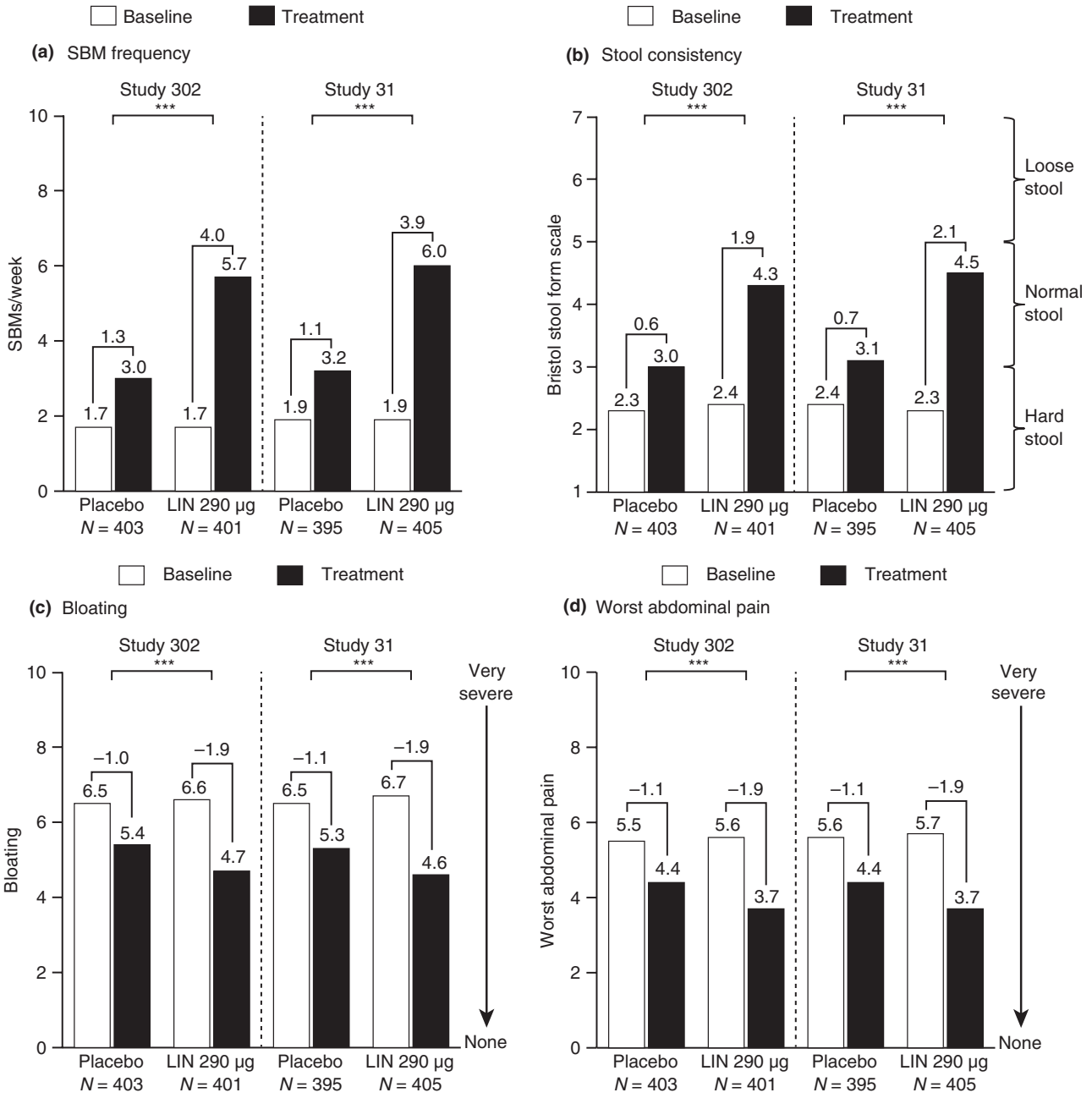

Figure 2 | The effect of linaclotide on main symptoms associated with IBS-C.[49, 50] Data shown are mean scores over the 2-week pre-treatment baseline period and mean scores for the first 12 weeks of treatment. Bloating and abdominal pain were rated on an 11-point scale from: 0 = 'none' to 10 = 'very severe'. Stool consistency was assessed using the Bristol Stool Formation Scale. ***$P < 0.0001$ (linaclotide vs. placebo, analysis of covariance), ITT population. IBS, irritable bowel syndrome; ITT, intent-to-treat; LIN, linaclotide; SBM, spontaneous bowel movement.

Table 4 | US Food and Drug Administration co-primary efficacy outcomes in linaclotide Phase 3 clinical studies[49, 50]

Endpoint	Study 31			Study 302		
	Placebo, $n = 395$	Linaclotide, 290 μg, $n = 405$	*P* value	Placebo, $n = 403$	Linaclotide, 290 μg, $n = 401$	*P* value
12-week abdominal pain and CSBM (+1) responder (%)	21.0	33.6	<0.0001	13.9	33.7	<0.0001
12-week abdominal pain responder (%)	27.1	34.3	0.0262	19.6	38.9	<0.0001
12-week CSBM (3 + 1) responder (%)	6.3	19.5	<0.0001	5.0	18.0	<0.0001
12-week abdominal pain and CSBM (3+1) responder (%)	5.1	12.1	0.0004	3.0	12.7	<0.0001

CSBM, complete spontaneous bowel movement.

In general, treatment effects with linaclotide were evident within the first week of treatment.[50, 59]

During the 4-week randomised withdrawal period, patients who were re-randomised to placebo after taking linaclotide for 12 weeks reported that the linaclotide-induced improvements in abdominal pain and CSBM frequency diminished to levels similar to those reported by patients in the placebo group over the treatment period.[50] As expected, patients who continued taking linaclotide continued to experience treatment benefits, and patients who switched from placebo to linaclotide felt benefits similar to levels experienced by patients who started on linaclotide during the 12-week treatment period. Importantly, there was no rebound effect after stopping linaclotide.[50, 60]

Treatment with both linaclotide and placebo improved health-related QoL.[59] However, improvements in the IBS-QoL overall score and the EuroQoL-5 dimensions (EQ-5D) Utility Index were significantly greater with linaclotide compared with placebo (Table 3). Treatment benefits with linaclotide were significant vs. placebo for all IBS-QoL subscale scores (dysphoria, body image, health worry, food avoidance, social reaction, sexual and relationships), except for 'interference with activity', with the largest differences between treatment groups in the 'body image', 'health worry' and 'food avoidance' categories.[59]

Study 302: 26-week randomised treatment period. In Study 302 (NCT00938717), 805 patients were randomised 1:1 to receive linaclotide 290 μg or placebo for 26 weeks. The patient demographics were similar to Study 31: most of the patients were white (78%), female (90%) and below the age of 65 years (95%, mean age 44 years).[49] As in Study 31, linaclotide was effective in treating IBS-C according to the co-primary EMA-specified endpoints: 54.1% of linaclotide-treated patients were 12-week abdominal pain/discomfort responders vs. 38.5% of placebo-treated patients, and 39.4% of linaclotide-treated patients were 12-week IBS degree-of-relief responders vs. 16.6% of placebo-treated patients.[59] Treatment effects were sustained over the 26-week treatment period (Table 5). Similar to results from Study 31, secondary efficacy outcomes assessing bowel and abdominal symptoms, such as the frequency of CSBMs and SBMs, stool consistency, severity of straining, bloating, abdominal pain and abdominal discomfort, were significantly improved by linaclotide treatment vs. placebo (Figure 2; Table 5). Linaclotide treatment also resulted in significant improvements vs. placebo according to the four co-primary endpoints based on the FDA guidelines (Table 4).[49] Again, treatment effects with linaclotide were evident within the first week of treatment.[49, 59]

In Study 302, linaclotide led to significantly larger improvements in the IBS-QoL overall score, the EQ-5D Utility Index and the EQ-5D Visual Analogue Scale score vs. placebo (Table 5).[59] For the IBS-QoL, improvements with linaclotide were significantly greater than improvements with placebo for all of the subscale scores. As in Study 31, the largest treatment differences were seen in the 'body image', 'health worry' and 'food avoidance' categories.[59]

Side-effect profile of linaclotide and safety data in the Phase 3 clinical studies. In both Phase 3 studies (a total safety population of 1607 patients), the overall incidence of adverse events was slightly higher in the linaclotide treatment groups than in the placebo groups.[49, 50] The most frequent adverse events with a greater incidence with linaclotide compared with placebo in the Phase 3 studies were diarrhoea, abdominal pain, flatulence, headache, viral gastroenteritis and abdominal distension.[61] Diarrhoea, which occurred in less than 20% of linaclotide-treated patients in the Phase 3 studies, can be considered to be a consequence of the therapeutic effect of

Table 5 | Summary of linaclotide efficacy outcomes in Study 302[49, 59]

	Placebo, n = 403	Linaclotide, 290 μg, n = 401	P value
Co-primary endpoints			
12-week abdominal pain/discomfort responder	38.5%	54.1%	<0.0001
12-week IBS degree-of-relief responder	16.6%	39.4%	<0.0001
Additional responder analyses			
26-week abdominal pain/discomfort responder	36.0%	53.6%	<0.0001
26-week IBS degree-of-relief responder	16.9%	37.2%	<0.0001
12-week sustained abdominal pain/discomfort responder	38.0%	53.6%	<0.0001
12-week sustained IBS degree-of-relief responder	15.6%	36.7%	<0.0001
26-week sustained abdominal pain/discomfort responder	33.3%	51.9%	<0.0001
26-week sustained IBS degree-of-relief responder	14.1%	33.2%	<0.0001
Change from baseline to Week 12 in:			
CSBM frequency rate	0.7	2.2	<0.0001
Stool consistency (BSFS)	0.6	1.9	<0.0001
Severity of straining	−0.7	−1.2	<0.0001
SBM frequency	1.3	4.0	<0.0001
Bloating	−1.0	−1.9	<0.0001
Abdominal pain	−1.1	−1.9	<0.0001
Abdominal discomfort	−1.1	−1.9	<0.0001
Abdominal fullness	−1.1	−2.0	<0.0001
Abdominal cramping	−1.1	−1.8	<0.0001
IBS-QoL	11.0	17.3	<0.0001
EQ-5D Utility Index score	0.05	0.09	<0.001
EQ-5D Visual Analogue Scale score	4.7	7.0	<0.01

BSFS, Bristol Stool Formation Scale; CSBM, complete spontaneous bowel movement; EQ-5D, EuroQoL-5 dimensions; IBS, irritable bowel syndrome; NS, not significant; QoL, quality of life; SBM, spontaneous bowel movement.

linaclotide driven by the pharmacological mode of action to relieve constipation (increased fluid secretion and accelerated colonic transit).[49, 50, 59] In both studies, approximately 90% of cases of diarrhoea were mild to moderate and around a quarter of patients who experienced diarrhoea discontinued from the studies due to this side effect. Approximately half of patients who experienced diarrhoea reported onset within the first week (Study 302) or the first 2 weeks of treatment (Study 31).[49, 50] In Study 302, most cases of diarrhoea in the linaclotide treatment group occurred during the first 12 weeks of the 26-week treatment period.[49] If patients discontinued treatment, most cases of diarrhoea resolved within a few days.[54] For patients with diarrhoea who continued treatment, approximately one third of cases were resolved within 1 week.[54]

In both studies, a subset of patients was analysed for systemic exposure to linaclotide or its main metabolite after 4 weeks of treatment. None of the 64 linaclotide-treated patients analysed in Study 31 showed quantifiable plasma levels of linaclotide (≥0.2 ng/mL) and 2 of 98 linaclotide-treated patients in Study 302 had plasma levels just above the detection limit (0.24 ng/mL for both). The active metabolite could not be detected in plasma samples in either study.[49, 50] However, the detection limit for the metabolite was 2.0 ng/mL, 10-fold higher than the linaclotide detection limit.

Current and future research

As IBS-C is a chronic condition and linaclotide is designed to be a long-term treatment, it is important to further establish the safety and efficacy of linaclotide in a larger population of patients over a longer period of time, i.e. beyond 26 weeks of treatment. Two open-label, Phase 3, 52-week safety studies of linaclotide have been conducted: NCT00765999 (1557 patients) and NCT00730171 (1743 patients). These studies enrolled more than 3300 patients with IBS-C or chronic constipation who had participated in previous Phase 2 or 3 linaclotide studies; results are not yet available.

Importantly, linaclotide showed efficacy not only in terms of constipation relief but also in terms of multiple other abdominal and bowel symptoms associated with IBS-C, including abdominal pain and discomfort. Mediation analysis of pooled data from Study 31 and Study 302 has shown that the improvements of abdominal pain symptoms were largely independent of constipation relief.[62] Hence, an interesting area to explore in future

studies would be potential benefits of linaclotide in patients with functional GI disorders other than IBS-C and chronic constipation, for example, patients with functional abdominal pain or patients with functional bloating. In addition, due to the rapid onset of the therapeutic effects of linaclotide, patients with IBS-M might benefit from linaclotide as an on-demand treatment to ease abdominal pain and constipation. In view of the fluctuating course of IBS, future clinical studies in this area should also provide information on a potential more flexible use of linaclotide as an intermittent, on-demand treatment for patients with IBS-C, vs. the continuous treatment regimen that has been investigated in previous studies. This may also be of interest for patients with IBS-C who benefit from linaclotide treatment but have to discontinue because they experience diarrhoea. As a constipation relief, linaclotide might be useful for patients with constipation due to aetiologies other than IBS; linaclotide has been studied in patients with chronic idiopathic constipation and is approved for this indication in the USA (at a lower dose of 145 μg), but not in Europe.

Intriguingly, in recent studies, GC-C signalling has also been implicated in suppressing intestinal tumourigenesis, suggesting that GC-C agonists might potentially be useful for the prevention or therapy of colorectal cancer.[63, 64] However, no clinical research has been carried out to evaluate this hypothesis.

CONCLUSIONS

Irritable bowel syndrome with constipation is a prevalent, functional bowel disorder that causes a substantial burden to patients and society.[65, 66] While a large armamentarium of treatment options for IBS-C is available, the majority of these options lack proven efficacy from clinical trial data and/or have unfavourable side-effect profiles. Prior to the approval of linaclotide, no licensed pharmacological treatments effectively relieved constipation and abdominal pain symptoms of IBS-C.

Linaclotide has been investigated in a comprehensive clinical trial programme and has been shown to be an effective therapy for IBS-C based on EMA-specified study endpoints assessing abdominal pain or discomfort and patient-reported relief from IBS symptoms. On the strength of these data, linaclotide is the first drug authorised by the EMA for the symptomatic treatment of moderate-to-severe IBS-C.[61] Furthermore, the efficacy of linaclotide in treating IBS-C according to study endpoints based on FDA guidelines has been shown for the same clinical studies, leading to the approval of linaclotide for treating IBS-C by the FDA.[67] Importantly, linaclotide not only improved clinical outcome measures but also had a positive effect on patients' QoL. Few other agents have been able to report treatment effects on QoL in patients with IBS-C. Data are available for lubiprostone, a chloride channel activator, which did not significantly improve IBS-QoL overall scores vs. placebo after 12 weeks of treatment,[34] and tegaserod, a 5-HT_4 agonist, which showed short-term improvements in IBS-QoL after 4 weeks of treatment.[68, 69] Linaclotide-treated patients reported improvements in QoL that were not only statistically significant vs. placebo, but, more importantly, the improvements seen in the EQ-5D utility index are considered to be clinically relevant in comparison with other chronic diseases.[70, 71]

In the Phase 3 clinical trials, linaclotide had an overall favourable safety profile and did not appear to be associated with any relevant systemic side effects. The main side effect of linaclotide was diarrhoea, which likely represents an extension of its pharmacological actions. Importantly though, similar levels of treatment satisfaction were reported by patients who experienced diarrhoea as a side effect of linaclotide and by linaclotide-treated patients without diarrhoea in the Phase 3 clinical trials.[72]

In conclusion, linaclotide, a first-in-class GCCA, is a promising and potentially important new drug with a novel, dual mechanism of action that can relieve the abdominal pain, bloating and constipation associated with IBS-C. Existing treatment options target single symptoms; this is reflected in current treatment guidelines, which recommend treatment options for individual symptoms associated with IBS. Due to a low oral bioavailability, linaclotide appears to be associated with a very low risk of relevant systemic adverse reactions. This may constitute an important consideration in view of the essentially benign natural course of IBS-C, which implies a very low tolerance for side effects. Linaclotide represents a completely new treatment concept and may in time change treatment approaches in IBS-C.

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Abbott/Abbvie, Almirall, Aptalis, Boehringer Ingelheim, Falk, Norgine, Pfizer, Shire and Solvay, and has received research funding from Abbott, Lilly, Norgine, Solvay and Steigerwald; is an employee of the Israelitic Hospital, Hamburg University Academic Hospital, Hamburg, Germany; owns no stocks and shares; and owns no patents. VS has served as a speaker, a consultant and an advisory board member for Alfa Wassermann, Almirall, Angelini, Aptalis, CM&D Pharma, Farmaderma, Ironwood, Italchimici, Janssen, Norgine, Shire, Takeda, Valeas and Zeria, and has received research funding from Alfa Wassermann, Almirall, Aptalis, Italchimici, Norgine, Shire, Takeda and Valeas; is an employee of University Hospital St. Orsola-Malpighi, University of Bologna, Bologna, Italy; owns no relevant stocks and shares; and owns no relevant patents.

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