CLINICAL INVESTIGATION

Linaclotide for irritable bowel syndrome with constipation: a review

Michael Arriaga[1]
& Eamonn MM Quigley*[,2]
[1]Department of Medicine, Houston Methodist Hospital, Weill Cornell Medical College, Houston, TX 77030, USA
[2]Department of Medicine & Division of Gastroenterology & Hepatology, Houston Methodist Hospital, Weill Cornell Medical College, Houston, TX 77030, USA
*Author for correspondence: equigley@tmhs.org

Irritable bowel syndrome (IBS) is a common disorder that poses a management challenge. IBS with constipation as the dominant bowel habit is a common phenotype and features abdominal pain, infrequent bowel movements or difficult defecation, bloating and distention, as major symptoms. While laxatives increase stool frequency, they have little impact on other symptoms; prior, more specifically targeted, therapies have been withdrawn because of adverse events. Prosecretory agents represent a new drug class that act locally and have minimal systemic absorption; linaclotide is the latest to obtain regulatory approval and provides significant relief of the cardinal symptoms of IBS-constipation. Linaclotide also accelerates colonic transit and animal data suggest a visceral analgesic effect. The main side effect has been diarrhea.

Keywords: constipation • diarrhea • intestinal secretion • irritable bowel syndrome • laxatives • linaclotide • lubiprostone • prokinetics • prosecretory agents

IBS-constipation: the clinical problem

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that affects from 10 to 15% of the adult population in the USA [1]. While many do not seek medical attention for their symptoms, a substantial minority of IBS sufferers experience symptoms which are so debilitating that they cause mental and physical anguish sufficient to impact on personal and professional life. As IBS is still commonly perceived as an 'insignificant' disorder which is poorly amenable to medical treatment, many affected individuals suffer in silence and self-manage using self-imposed changes in diet and/or lifestyle and over-the-counter and 'alternative' remedies in an attempt to combat the symptoms they encounter. Consequently, the direct and indirect medical and societal costs associated with IBS are substantial [2]. Despite costs to the individual and the community associated with the disorder, treatment options have been limited, have largely focused on the alleviation of individual symptoms and, up until recently, were, for the most part, poorly supported by high quality clinical trials.

A major challenge to the development of effective therapies for IBS is that there is no diagnostic test or validated biomarker for IBS; its diagnosis rests, therefore, entirely on clinical grounds [3]. Over the past several decades, several efforts have been made to codify and standardize the diagnosis of IBS and a number of diagnostic approaches or criteria have emerged. Among these the most widely accepted in the realm of clinical research are those developed through the consensus process initiated and sustained by the Rome Foundation. The most current, third, iteration of these Rome Criteria, Rome III (now over 9 years old and about to be updated) represents the internationally accepted standard for the definition of IBS subjects for inclusion in clinical trials and other clinical studies [4]. In clinical practice, however, these criteria are infrequently applied with an earlier instrument, the Manning Criteria, still representing a closer approximation to the approach that most physicians take to the diagnosis of IBS in their everyday practice [5,6]. Most primary care physicians suspect IBS on the basis of certain symptoms but rarely utilize formal

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criteria in the diagnosis and continue to employ some basic serological tests to screen for other diagnoses and frequently refer to gastroenterologists to confirm the diagnosis [7]. It is worth noting that some symptoms regarded as pathognomonic of IBS in clinical practice and of considerable distress to sufferers, such as bloating and distension, are not even included as obligate components of the Rome definition. While one must be mindful of the Rome criteria in evaluating clinical trials, one must be equally aware of the fact that any new medication or other intervention developed through a clinical trial process employing Rome III will be applied to a patient population who may well not fulfill these same criteria. Expectations created by results in a Rome III defined population may not be met and unexpected adverse events encountered, when a new pharmacological agent is prescribed in a wider IBS population.

What are the Rome III criteria? According to Rome III, IBS is defined on the basis of the presence of:

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following:

- Improvement with defecation;
- Onset associated with a change in frequency of stool;
- Onset associated with a change in form (appearance) of stool.

These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis [4].

It is readily apparent that pain is a central feature of IBS and has become a obligatory outcome measure in all trials of IBS that seek to achieve regulatory approval in major markets. However, IBS is far from being a mono-symptomatic entity; in individual patients, disturbed bowel function, bloating and/or distention may loom large in their symptom experiences and must, therefore, be addressed by a therapy that seeks to provide global relief in IBS; a tall order, indeed. With regard to bowel function, clinical experience led to the recognition that IBS sufferers could be loosely categorized according to dominant bowel habit; constipation, diarrhea and alternating. Prior to Rome III, subtyping was based on symptoms alone; Rome III introduced a degree of objectivity to this process by defining dominant bowel habit according to the Bristol stool scale [8]; a patient's description of stool form that has been shown to correlate with colon transit. In Rome III, therefore, IBS was subtyped as either constipation (IBS-C) or diarrhea-predominant (IBS-D), mixed type (IBS-M) and unclassified (IBS-U). This approach was especially appealing to those who had developed new drugs whose mechanism of action predicted a particular benefit among those with either IBS-C or IBS-D.

IBS-C: traditional therapeutic approaches

Traditional mainstays of the treatment of IBS have included alterations in diet, fiber supplementation, probiotics, antispasmodics, antidepressants, serotonergic agents and a variety of psychological therapies [9]. For IBS-C, specifically, additional approaches have included laxatives, prokinetics and, most recently, prosecretory agents [9].

Dietary modification

Dietary changes are often implemented by IBS sufferers in an attempt to curb symptoms that they feel can be attributed to food, as well as perceived food intolerances or allergies. While few of these dietary interventions have been subjected to rigorous investigation, two, the low FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) and a gluten-free diet have been the subject of recent studies [10–13]. In comparison to a standard diet, the low FODMAPs diet was associated with significant symptomatic benefits [8]; results with a gluten-free diet have been less consistent [11–13]. Both approaches require further high quality studies before one can accurately assess their place in the longer-term management of IBS-C, specifically. Thus, data on gluten-free diets are largely derived from subjects with IBS-D and the impact of a low FODMAPs diet on constipation is unclear.

Fiber supplementation

For decades, IBS sufferers and, especially, those with constipation were recommended to increase dietary fiber or take fiber supplements. While there seems little doubt that fiber and fiber supplements can increase stool frequency, the impact of fiber supplementation on IBS, in general, is more complex. It has been clear for some time that fiber and insoluble fiber, in particular, can exacerbate the symptoms of bloating, distension and abdominal discomfort. For example, in a 12-week randomized placebo-controlled study, Bijkerk and colleagues found that 57% of patients randomized to consume 10 g of the soluble fiber supplement psyllium reported adequate symptom relief in comparison to 35% of those on placebo. In contrast, those consuming 10 g of the insoluble fiber in the form of wheat bran reported symptomatic benefits only during the third month of treatment. Furthermore, at the end of the 12 weeks of the study, self-reported quality-of-life

scores were similar between placebo and both fiber groups [14]. In a recent meta-analysis, benefits for fiber in IBS were limited to soluble fiber and were related largely to improvements in bowel function rather than in pain or discomfort [15].

Approaches to modify the microbiota

Given the high frequency of bloating and distension in IBS, in general and in IBS-C, in particular, attention has focused of late on therapeutic strategies that impact on the gut microbiota. While strategies such as antibiotics, prebiotics and probiotics have been largely directed towards those with IBS-D or prominent bloating, there is some evidence to suggest that certain probiotics may benefit those with IBS-C [16]. In IBS-C, constipation has been linked to the presence of a methanogenic flora; randomized controlled trials of antibiotic therapy in this scenario have yet to be reported [17].

Antispasmodics

For well over half a century, antispasmodics have played a central role in the management of pain and discomfort in IBS and, while high quality studies are scarce, these agents, as a class, seem to be effective in the short-term relief of these symptoms [9]. There is, however, no evidence to support an impact on the natural history of IBS and most, if not all, will by virtue of their mode of action, tend to exacerbate constipation; thereby, limiting their usefulness in the long-term treatment of IBS-C.

Antidepressants

Based, initially, on the association of IBS with anxiety and depression and, later, on the belief that these agents exerted a visceral analgesic effect, a variety of antidepressants and anxiolytics have been used in the management of IBS. Both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have proven, overall, to be effective in providing global symptom and pain relief [18]. Most studies did not specify IBS subtype, with only one specifically recruiting IBS-C subjects. In this particular study, fluoxetine reduced abdominal discomfort and bloating, increased the frequency of bowel movements and was associated with a low rate of adverse events [19]. In contrast, tricyclic compounds should be used with caution, if at all, in IBS-C given their known anticholinergic actions.

Laxatives

Though laxatives have been extensively used on an empirical basis in the treatment of IBS-C, only polyethylene glycol has been subjected to any degree of rigorous assessment and here the evidence indicates some impact on stool frequency but none on global symptoms or pain/discomfort [20].

Prokinetics

The neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) is involved in many aspects of gastrointestinal function, including motility, secretion and visceral sensation. Specifically, activation of serotonin subtype 4 (5-HT4) receptors enhances intestinal secretion and accelerates transit [21]. While studies with mixed 5-HT3 antagonists and 5-HT4 agonists, such as cisapride [22], mosapride [23] and renzapride [24], failed to provide consistent results in IBS, tegaserod, an amino-guanidine-indole, and a partial selective agonist of the 5-HT4 receptor was approved in 2002 by the US FDA for use in women with IBS-C based on positive clinical trials [25]. Subsequent concerns related to possible cardiovascular effects led to its worldwide withdrawal from the marketplace. While more selective 5-HT4 agonists such as prucalopride and velusetrag have demonstrated efficacy in chronic idiopathic constipation [9] and the former has been approved in several countries for this indication, neither has been studied, as yet, in IBS-C.

Prosecretory agents

Given the issues described above that arose related to systemic side effects with novel systemically absorbed, pharmacological therapies for IBS, in general, attention has recently focused on approaches that exert their effects directly on the gut and are minimally absorbed. Of these, the first to gain approval was lubiprostone, a bicyclic fatty acid [26], which activates type 2 chloride channels on the apical surface of the intestinal epithelium leading to the secretion of chloride and water into the intestinal lumen [27]. This lubricates stool and facilitates its passage through the large intestine. Studies of lubiprostone in IBS-C demonstrated a significant benefit for lubiprostone over placebo in overall symptom relief, though the effect was modest in size (responder rate for lubiprostone vs placebo in the two pivotal studies; 17.9 vs 10.1%) [28]. Diarrhea (overall frequency 6%) and nausea [8%] were both more common in lubiprostone – compared with placebo-treated patients [27,28].

Linaclotide

Basic pharmacology

Linaclotide is a synthetic peptide composed of 14-amino acids and structurally related to the guanylin peptides guanylin and uroguanylin, the naturally occurring agonists of the guanylate–cyclase (GC-C) receptor, which play a physiological role in intestinal

fluid and electrolyte balance [29]. Interestingly, linaclotide is also structurally similar to the ST peptides of *Escherichia coli* that cause diarrhea [30].

Orally administered linaclotide is metabolized, in the gut, into destyrosine, a 13-amino acid active metabolite. *In vitro* studies indicated that both molecules were resistant to digestion by chymothrypsin and aminopeptidase [31]. Linaclotide binds to and activates the GC-C receptor located on the luminal surface of colonic epithelial cells in a pH-independent manner [32]. This, in turn, leads to an increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP). cGMP activates protein kinase II, which phosphorylates and activates the cystic fibrosis transmembrane conductance regulator (CFTR) on the apical surface of colonic epithelial cells [29–31]. Activation of CFTR enhances secretion of bicarbonate and chloride ions, leading to inhibition of sodium absorption and increased water flow into the intestine. In animal models, linaclotide was also shown to produce a GC-C-dependent acceleration of gastrointestinal transit [29,31]. Of considerable relevance to its potential role in IBS-C, linaclotide also demonstrated antinociceptive effects in a rodent model. This independent effect, though also mediated via activation of GC-C receptors, seemed to result from the extracellular transport of cGMP into the subepithelial space where visceral afferents reside and led to a reversal of colonic hypersensitivity [33].

Phase I studies

In two studies, linaclotide was well tolerated in 30 healthy volunteers exposed to either single doses ranging from 30 to 3000 µg (total peptide content) or to repeated doses ranging from 30 to 1000 µg once daily for 7 days. Linaclotide showed dose-related effects on stool consistency and weight in the absence of detectable levels of linaclotide or destyrosine in serum [34].

In a third, open-label study in healthy volunteers, 290 µg of linaclotide was administered once daily for 7 days followed by a dose of a 2897 µg on the 8th day [35]. When given immediately after a high-fat meal, linaclotide was more likely to lead to more frequent and looser stools than if given while still fasting. This observation led to the subsequent recommendation that linaclotide be administered 30 min before a meal. Importantly, as previously demonstrated in animal models, oral bioavailability was very low; linaclotide was detected in plasma only after the 8th day of dosing with 2897 µg and then only in two of 18 study participants; less than one nanogram/milliliter of linaclotide was detected in each instance [31]. Recovery in feces during the 7 days of dosing at the 290 µg level averaged 3–5% of the administered dose with virtually all as the active metabolite destryosine. On the 8th day, 0.4% of the 2897 µg dose was recovered as linaclotide in the feces. *In vitro* studies have shown that linaclotide and its active metabolite, destyrosine, had no effects on the CYP450 system. Thus, due to its intestinal location of action and lack of systemic absorption, the dosing of linaclotide would not need to be altered regardless of concerns of hepatic metabolism or renal clearance [35].

Phase II studies

The first such involved 36 women with IBS-C who were randomized in a double-blind placebo-controlled study to receive either placebo or 100 µg or 1000 µg of linaclotide for 5 days. Both doses led to significant effects on stool frequency, consistency, ease of passage and time to first bowel movement. While bloating, urgency and flatulence were numerically more frequent among those on active agent, these differences were not statistically significant from placebo [36]. Importantly, this study demonstrated a significant acceleration of colonic transit, an effect not observed by the same investigators when they had previously studied lubiprostone [37].

In a pilot study, 42 patients (37 female) were randomly assigned to 2 weeks' treatment with linaclotide in doses of 100, 300 or 1000 µg or placebo [38]. Linaclotide produced a dose-dependent increase in complete spontaneous bowel movements (CSBMs; frequency per week, increase from base-line: range 2.2–3.2 for linaclotide vs 1.3 for placebo) and improved and dose-dependent scores for stool consistency and straining.

In a placebo controlled, 12-week Phase IIb study, the efficacy and safety of 12 weeks of treatment with linaclotide in doses of 75, 150, 300 and 600 µg were analyzed in 419 patients with IBS-C [39]. Participants receiving linaclotide reported improvements in abdominal pain scores (mean reduction in abdominal pain score on a 5-point scale for the linaclotide doses 0.71, 0.71, 0.90 and 0.86 vs 0.49 for placebo), as well as in the frequency of spontaneous bowel movements (SBMs) and CSBMs. Importantly, these effects were seen in the first week of treatment, were sustained throughout the course of the study and returned to base-line levels during the 2-week post-treatment observation period. Diarrhea occurred in a dose-dependent manner in between 11 and 18% of linaclotide-treated in comparison to 1% of placebo-treated patients. The diarrhea was, for the most part, reported as mild to moderate, with most instances occurring within the first 4 days of linaclotide administration. In assessing the benefit-risk ratio, the 300 µg dose seemed optimal and was, therefore, further evaluated in Phase III studies.

Phase III studies

Two multicenter, randomized, double-blind, placebo-controlled studies were performed using identical primary end points and conducted in the USA and Canada [40,41] (Table 1).

Both trials [40,41] were structured to comply with end points recommended by the FDA for IBS clinical trials and included four coprimary efficacy end points:

- 1. The FDA's primary end point for IBS-C: This defined a responder as a patient who had improvement of ≥30% in average daily worst abdominal pain score and an increase by ≥1 CSBM from baseline (same week) for at least 50% of weeks assessed;
- 2. An improvement of ≥30% in abdominal pain*;
- 3. ≥3 CSBMs and an increase of ≥1 CSBM from baseline*;
- 4. A combined end point that defined a responder as a patient who met both 2 and 3 in the same week*.

Each of these responder definitions had to be met for at least 9 of the first 12 weeks of the initial treatment period.

In the trial conducted by Rao and colleagues [40], 803 participants were randomized to receive linaclotide 290 µg (equivalent to 300 µg total peptide content) or placebo for 12 weeks. Baseline characteristics of the 803 participants were similar [40]. 90% were female and the mean age was 43 years old. On completion of the 12 weeks of treatment, subjects initially randomized to linaclotide were re-randomized to receive either placebo or linaclotide for a further 4 weeks, while those who were initially assigned to placebo were all now treated with 290 µg of linaclotide for 4 weeks.

In the initial 12-week period, participants randomized to receive linaclotide demonstrated statistically significant improvements in all primary and secondary efficacy end points. 33.6% of linaclotide-treated patients versus 21.0% of placebo-treated patients met the FDA end point. 50.1% of linaclotide-treated patients versus 37.5% placebo-treated patients reported a decrease of ≥30% in abdominal pain and 48.6 vs 29.6%, respectively, an increase of ≥1 CSBMs per week above baseline for at least 6 of the 12 weeks of treatment. Treatment effects were evident within the first week of treatment and sustained over the course of the 12-week treatment period by those in the linaclotide treatment group. Moreover, at the end of 12-week treatment period, all secondary end points were met for linaclotide-treated patients compared with placebo-treated patients; with a mean decrease from baseline (on an 11-point scale) for worst abdominal pain of

Table 1. Pivotal Phase III studies of linaclotide in irritable bowel syndrome with constipation.

Study (n)	US FDA coprimary end point			Pain component of FDA coprimary end point			Stool frequency component of FDA coprimary end point			Other primary end point			Ref.
	Lin (%)	Pla (%)	NNT	Lin (%)	Pla (%)	NNT	Lin (%)	Pla (%)	NNT	Lin (%)	Pla (%)	NNT	
Chey *et al.* (n = 804)	33.7	13.9	5.1	48.9	34.5	7.0	47.6	22.6	4.0	12.7	3.0	10.3	[41]
Rao *et al.* (n = 800)	33.6	21	8.0	50.1	37.5	7.9	48.6	29.6	5.3	12.1	5.1	14.2	[40]

Lin: Linaclotide; NNT: Number needed to treat; Pla: Placebo.
Data taken from [40,41]. For details on end points, please see text.

1.9 points for linaclotide-treated compared with 1.1 for placebo-treated patients ($p < 0.0001$) and also with increases seen in weekly CSBM rates.

These results were maintained during the 4-week randomized withdrawal period. In particular, patients who were randomized from the linaclotide treatment group to the placebo group experienced an increase in worst abdominal pain and a decrease in CSBM rates to levels similar to those of placebo-treated patients; whereas, those who continued to take linaclotide sustained their improvements in worst abdominal pain ($p < 0.05$) and CSBMs ($p < 0.001$).

The major adverse event encountered was diarrhea which was reported by 19.5% of linaclotide-treated subjects compared with 3.5% of placebo-treated patients. The majority of the 79 linaclotide-treated patients who experienced diarrhea reported it within the first 2 weeks of treatment; most (71 of 79) reported mild–moderate diarrhea, with none experiencing diarrhea-related clinical sequelae. 5.7% of linaclotide-treated patients discontinued the trial due to diarrhea, with only 0.3% discontinuing treatment in the placebo-treated group due to diarrhea. Other adverse events included abdominal pain (5.4 vs 2.5% in linaclotide vs placebo, respectively) and flatulence (4.9 vs 1.5%). During the randomized withdrawal period, the incidence of diarrhea was 11.7% in placebo-linaclotide patients, 1.9% in linaclotide-linaclotide patients and 0.6% in linaclotide-placebo patients.

The second study, conducted by Chey and colleagues [41], was a multicenter, randomized, double-blind, placebo-controlled trial in which 805 patients were randomized to receive linaclotide 290 µg or placebo for 26 weeks [41]. Patient demographics and baseline characteristics were similar in both groups with most participants again being white females with an average age of 44 years. 33.7% of linaclotide patients versus 13.9% of placebo met the FDA end point requirements over the first 12 weeks of treatment ($p < 0.001$; number needed to treat [NNT] = 5.1). 48.9% of linaclotide-treated patients versus 34.5% placebo-treated patients reported a decrease of ≥30% in worst abdominal pain from baseline for ≥6/12 or ≥13/26 weeks of the treatment period ($p < 0.001$; NNT = 7). Moreover, 47.6% of linaclotide-treated patients versus 22.6% placebo-treated patients reported an increase of ≥1 CSBM per week above baseline for ≥6/12 or ≥13/26 weeks of the treatment period ($p < 0.001$; NNT = 4). With regard to other efficacy parameters, 42.9% of linaclotide-treated patients versus 23.8% placebo-treated patients reported a decrease of ≥30% in abdominal bloating and pain from baseline for ≥6/12 or ≥13/26 weeks ($p < 0.001$). SBMs occurred within 24 h after the first dose in 65.6% of linaclotide-treated patients versus 40.4% placebo-treated patients, with 55.4% of linaclotide-treated patients maintaining an SBM rate increase of ≥2/week above their baseline frequency for at least 50% of all treatment weeks. At the end of the 26-week treatment period, linaclotide-treated patients had achieved a 47% reduction in their worst abdominal pain and a frequency of 4.8 SBMs/week compared with 25% and 2.5 SBMs/week, respectively, for placebo-treated patients ($p < 0.001$). In this study, as with the other Phase III trial, diarrhea was the most commonly reported adverse event; occurring in 19.7% linaclotide- and 2.5% of placebo-treated patients. Of the 79 linaclotide-treated patients who experienced diarrhea, 48.1% reported it within the first week of treatment and 75.9% within the first 4 weeks of starting linaclotide. 4.5% of linaclotide-treated patients discontinued the trial due to diarrhea, with only one placebo-treated patient discontinuing treatment due to diarrhea. Other adverse events in the study included abdominal pain (4.5 vs 4.0% in linaclotide vs placebo, respectively) and flatulence (3.7 vs 2.2% in linaclotide vs placebo, respectively).

Summary of clinical studies

In reviewing these pivotal trials together with preclinical and Phase I and II data, it is evident that linaclotide exerts a statistically and clinically significant effect on the core symptoms of IBS-C: constipation, abdominal pain and bloating. During the Phase III trials, this effect was sustained for up to 26 weeks and symptoms rapidly recurred once linaclotide was withdrawn. Not unexpectedly, given its method of action, diarrhea was the main side effect; however, in these clinical trials at least, diarrhea was rarely of sufficient severity to result in withdrawal from the study. Interestingly, and in contrast to lubiprostone, nausea was not a significant problem. It is also interesting to note that the time course of the effects of linaclotide on bowel symptoms and pain differed with the former being of rapid onset and the latter being most evident after 4–6 weeks, suggesting, as *in vivo* studies had hinted, that these are independent effects.

Conclusion

Linaclotide represents a good example of the translation of basic intestinal physiology to clinical practice and offers an effective and generally safe agent for the management of a common and, at times, intractable disorder, constipation-predominant irritable bowel syndrome.

Future perspective

What will be the place of linaclotide in clinical practice? While it certainly has many attractive features

including efficacy on cardinal symptoms and lack of systemic toxicity, a number of questions remain. IBS-C is not a short-term disorder; will benefits for linaclotide 'wear off' over time? If treatment is suspended, for whatever reason, will retreatment be effective? Will diarrhea become a treatment limiting issue if indication creep occurs in populations with a more mixed bowel habit or when, as will inevitably happen for some, an IBS-C subject naturally shifts into IBS-M mode? Studies of lubiprostone and linaclotide did not involve an active comparator, such as a fiber supplement or laxative. While one can argue that there is little evidence that either of these latter agents exerts global benefits in IBS-C, it is also clear that high quality studies of these cheap and readily available agents are scanty and head-to-head comparisons with these over-the-counter medications could be demanded by those who pay for medication and all who are concerned about the costs of medical care.

Even though it is certainly not a panacea, linaclotide will be used in the management of IBS-C; its positioning in the treatment algorithm being determined by both clinical (predictors of response) and nonclinical (costs, restrictions on use imposed by insurance companies and other payors, alternative therapies available) factors. Given the occurrence of diarrhea with linaclotide in carefully selected IBS-C subjects and the likely sensitivity of mixed (alternating) IBS subjects to this side effect, the impact of lower doses should be evaluated in this patient group. If the visceral analgesic effects of linaclotide are confirmed in man, the potential impact of this therapy in other functional gastrointestinal disorders which feature pain (noncardiac chest pain and functional dyspepsia, for example) will merit exploration.

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Executive summary

- Irritable bowel syndrome is a common and, for some, disabling disorder that can impose considerable personal and societal costs.
- Traditional therapeutic approaches, such as laxatives are, for the most part, poorly supported by high-quality evidence.
- Systemically active pharmacological approaches, such as prokinetics, have been bedeviled by adverse events.
- Luminally directed therapies, as illustrated by lubiprostone, showed considerable promise and led to further investigation of this approach.
- Linaclotide is structurally related to guanylin and uroguanylin, the naturally occurring agonists of the guanylate–cyclase receptor.
- Linaclotide, a guanylate–cyclase agonist, promotes chloride and fluid secretion through activation of the cystic fibrosis transmembrane conductance regulator.
- Linaclotide accelerates colonic transit and has been shown to exert a visceral analgesic effect in animal studies.
- In Phase III studies, linaclotide produced clinically significant beneficial effects on the cardinal symptoms of irritable bowel syndrome-constipation.
- The main side effect of lincalotide is diarrhea.

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