

# Linacotide for irritable bowel syndrome with constipation: integrating real-world evidence into the therapeutic puzzle

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## Abstract

Irritable bowel syndrome with constipation (IBS-C) is a common subtype of functional bowel disorder associated with substantial symptom burden and reduced quality of life. Management typically begins with dietary and lifestyle modification, laxatives, and antispasmodics; however, many patients experience inadequate relief, underscoring the need for more effective therapies.

Linacotide, a synthetic guanylin analog, is an established treatment for IBS-C. By activating guanylate cyclase-C (GC-C) receptors on intestinal epithelial cells, it promotes intestinal fluid secretion, accelerates transit, and alleviates visceral hypersensitivity. Randomized controlled trials have demonstrated its efficacy and favorable safety profile, with mild-to-moderate diarrhea and abdominal pain being the most common adverse events. Because clinical trial populations may not fully reflect real-world patient diversity, real-world evidence (RWE) provides valuable complementary data. This review summarizes current RWE on linacotide in IBS-C, integrating findings from multiple studies to present a comprehensive view of its effectiveness and safety in routine clinical practice. (*Acta gastroenterol belg.*, 2026, 89, 65-77).

**Keywords:** Linacotide, Irritable bowel syndrome, Constipation, Guanylin, Guanylate cyclase receptor.

## Introduction

Irritable bowel syndrome with constipation (IBS-C) is the subtype of IBS characterized by predominant abdominal pain and infrequent bowel movements (1). Its true prevalence is uncertain, as nearly half of affected individuals remain undiagnosed; however, about one in three diagnosed IBS cases is IBS-C (2–3). The disorder arises from multifactorial mechanisms involving genetic predisposition, altered motility, visceral hypersensitivity, disturbed brain–gut signaling, and psychosocial factors (4). Diagnosis relies on the Rome IV symptom-based criteria, provided no alarm features suggest another cause (Table 1) (1). Although non–life-threatening, IBS-C significantly affects quality of life and contributes to increased healthcare utilization and costs (5–7).

Management aims to relieve symptoms and improve health-related quality of life (HRQoL). First-line approaches include reassurance, lifestyle and dietary modifications—such as hydration, fiber intake, and physical activity—and, if needed, laxatives or antispasmodics (8). Yet, responses vary, and many patients experience persistent symptoms, emphasizing the need for targeted therapies. Recent research has focused on correcting key pathophysiologic disturbances, such as impaired secretion, barrier dysfunction, and visceral

hypersensitivity, leading to novel treatment options (9).

Linacotide, a synthetic peptide structurally related to guanylin, uroguanylin, and bacterial heat-stable enterotoxin, acts by activating guanylate cyclase-C (GC-C) receptors on enterocytes. This enhances chloride and bicarbonate secretion, accelerates transit, and reduces pain signaling. Randomized controlled trials across the United States and Asia have demonstrated its efficacy and safety, resulting in approval by the FDA, EMA, PMDA, and NMPA (10–15). However, translating clinical trial outcomes to daily practice remains complex (16). Real-world evidence (RWE) complements trial data by reflecting diverse patient populations, routine care settings, and long-term outcomes (17). This review summarizes current RWE on linacotide in IBS-C, integrating data from multiple sources to provide a practical understanding of its real-world effectiveness and safety.

## Search Strategy

A comprehensive search of PubMed, Cochrane Library, MEDLINE, Scopus Clinical Trial Register, and Web of Science identified studies on linacotide published up to January 2023. The MeSH terms “linacotide,” “irritable bowel syndrome,” and “constipation” were used individually and in combination with “AND” and “OR.” Two authors (A.M. and K.A.) independently conducted the search and manually screened references and conference abstracts from DDW, UEGW, and ECCO. Of 364 records retrieved, duplicates, non-English, and irrelevant studies were excluded, resulting in 89 publications for inclusion.

## Targeting GC-C for managing IBS-C

Guanylate cyclase-C (GC-C) is a transmembrane receptor encoded by the GUCY2C gene with intrinsic

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Table 1. — Rome IV diagnostic criteria for constipation-predominant Irritable Bowel Syndrome (IBS-C).

ADULTS
Recurrent abdominal pain $\geq 6$ months before diagnosis, associated with $\geq 2$ of the following, $\geq 1$ day per week in the last 3 months:
- Related to defecation - Associated with a change in frequency of stool - Associated with a change in form of stool corresponding to Bristol stool type 1 or 2
CHILDREN
Abdominal pain $\geq 4$ days per month, for $\geq 2$ months before diagnosis with $\geq 1$ of the following:
- Related to defecation - Associated with a change in frequency of stool - Associated with a change in form of stool corresponding to Bristol stool type 1 or 2

guanylate cyclase activity. It belongs to a family of seven mammalian guanylate cyclases that regulate gastrointestinal secretion via cyclic nucleotide signaling. GC-C was first identified in the 1970s as the cellular target of bacterial heat-stable enterotoxins causing severe infantile diarrhea (18–19). Its endogenous ligands, guanylin and uroguanylin—encoded by GUCA2A and GUCA2B—were later discovered and are short peptides stabilized by disulfide bonds (20–21). Secreted locally in the gut, they act through autocrine and paracrine mechanisms in a pH-dependent manner: uroguanylin predominates in the proximal small intestine, whereas guanylin is more active in the distal colon (22–24).

Ligand binding to GC-C converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), activating downstream pathways involving cGMP-dependent kinases, cyclic nucleotide-gated channels, and phosphodiesterases. These stimulate CFTR channels, increasing chloride and bicarbonate secretion and promoting intestinal fluid flow and motility (25). The physiological relevance of this pathway has been confirmed in GUCY2C loss-of-function models, which show defective electrolyte transport and obstruction (26–30).

Beyond fluid regulation, GC-C maintains epithelial barrier integrity and modulates visceral sensation. It stabilizes tight junctions by suppressing myosin light chain kinase and preserving the expression of junctional proteins such as claudin-2, occludin, and junctional adhesion molecule-A (31). Moreover, GC-C activation promotes basolateral cGMP efflux via MRP4 and MRP5 transporters, reducing submucosal neuronal excitability and visceral pain (32–34). Given its central roles in secretion, motility, barrier function, and nociception, GC-C activation represents a rational therapeutic target in IBS-C (35).

### GC-C activation and linaclotide

Linaclotide is a synthetic oligopeptide with a molecular weight of 1526.8, specifically engineered

to structurally and functionally mimic the endogenous peptides guanylin and uroguanylin. It consists of 14 amino acids—cysteine, glutamic acid, tyrosine, asparagine, proline, alanine, threonine, and glycine—arranged in sequence and stabilized through three intramolecular disulfide bonds linking Cys(1) to Cys(6), Cys(2) to Cys(10), and Cys(5) to Cys(13) (36) (Figure 1). The additional disulfide linkage, which distinguishes linaclotide from its natural ligands, confers substantially greater molecular stability and enhances its affinity for the guanylate cyclase-C (GC-C) receptor, with binding potency estimated to be 10–100 times higher than that of guanylin or uroguanylin (37–39).

### Pharmacologic properties of linaclotide

Linaclotide is administered orally at a recommended dose of 290  $\mu$ g once daily (14,15). Unlike its endogenous counterparts, it remains stable under gastric conditions for more than three hours, enabling a dose-dependent pharmacologic effect through its active metabolite, des-tyrosine (MM-419447), generated in the small intestine after cleavage of the Tyr(14) residue in its C-terminal region. Both linaclotide and its metabolite are rapidly degraded within about one hour, with only 3–5% of the parent compound recovered in feces (40).

Because of its large molecular size and hydrophilic nature, linaclotide is not absorbed across the intestinal epithelium by passive diffusion, resulting in minimal systemic exposure. Its limited absorption precludes interaction with metabolic enzymes or transport systems, including cytochrome P450 isoenzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5), intestinal or hepatic enzymes, and efflux or uptake transporters such as BCRP, MRP2–4, OATP1B1/1B3/2B1, PEPT1, and OCTN. This pharmacologic profile supports its excellent safety and compatibility with common drugs such as phenytoin, phenobarbital, and omeprazole (10–12,43).

Food intake may affect tolerability. In a crossover study of 18 healthy volunteers, gastrointestinal adverse events occurred more frequently when linaclotide was taken immediately after a high-fat meal. Accordingly,

the drug should be administered on an empty stomach, preferably 30 minutes before the first meal of the day (10–12).

### Insights from clinical trials

Table 2 summarizes the pivotal clinical trials evaluating linaclotide, which have elucidated its mechanism of action and confirmed its therapeutic efficacy in the management of IBS-C. The principal findings of these studies are discussed in the subsequent section.

### Effect on human gastrointestinal (GI) physiology

The physiological effects of linaclotide on the gastrointestinal (GI) tract were initially evaluated in preclinical studies using animal models, which demonstrated its ability to enhance intestinal secretion and transit while reducing visceral sensitivity (10–12,41). Its effects on human GI physiology were subsequently examined after the drug received regulatory approval for the treatment of IBS-C.

To date, two human studies have assessed these mechanisms. In the first, Farmer et al. investigated 13 patients with IBS-C to evaluate the impact of linaclotide on cecal pH—an indicator of fermentation—and on GI motility. Participants received linaclotide for 28 days and underwent motility testing using a wireless motility capsule at baseline and follow-up. The investigators observed significant changes in pH at the ileocecal junction ( $-2.4 \pm 0.2$  vs.  $-2.1 \pm 0.4$ ;  $P = 0.01$ ) and cecum ( $5.2 \pm 0.2$  vs.  $5.5 \pm 0.3$ ;  $P = 0.02$ ), along with a reduction in colonic transit time (2650 [2171–4038] vs. 1757 [112–3011] minutes;  $P = 0.02$ ), while gastric emptying and small bowel transit remained unchanged (42).

In a subsequent study, Rao et al. examined the effect of linaclotide on visceral hypersensitivity in 39 patients meeting Rome III criteria for IBS-C. Participants were randomized (2:1) to linaclotide or placebo for 10 weeks and underwent bidirectional gut–brain axis assessment via anorectal electrical and transcranial/trans-spinal–anorectal magnetic stimulation. Linaclotide significantly prolonged recto-cortical latencies without altering efferent signaling, thereby improving rectal hypersensitivity (43). Collectively, these findings confirmed that linaclotide's mechanism of action in humans parallels observations from preclinical models.

### Therapeutic Dose Range

The therapeutic dose range of linaclotide was defined through dose-finding studies in North America and Japan. In a Phase I randomized, double-blind, placebo-controlled study involving 48 healthy volunteers, doses of 30–1000  $\mu\text{g}$  were tested. The 1000  $\mu\text{g}$  dose significantly increased stool frequency and weight and improved stool consistency (12).

A subsequent Phase II trial in 36 women with Rome II IBS-C compared 100  $\mu\text{g}$  and 1000  $\mu\text{g}$  daily doses versus placebo for five days. Gastrointestinal transit scintigraphy showed that 1000  $\mu\text{g}$  markedly accelerated ascending colon emptying ( $P = 0.004$ ) and overall colonic transit at 48 hours ( $P = 0.01$ ), with corresponding improvements in stool frequency, consistency, and ease of passage (44).

These results informed the design of a large multicenter Phase IIb trial including 420 patients with Rome II IBS-C randomized to linaclotide 75–600  $\mu\text{g}$  or placebo for 12 weeks. All doses improved spontaneous and complete spontaneous bowel movements (SBMs, CSBMs), stool consistency, and straining versus placebo, with the greatest benefit at 300  $\mu\text{g}$ . Symptom relief appeared within the first week and was sustained throughout treatment (45). This evidence established the 300  $\mu\text{g}$  dose—marketed as 290  $\mu\text{g}$ —for further clinical development in Western populations.

In Japan, Fukudo et al. conducted a Phase II trial in 559 patients meeting Rome III criteria for IBS-C. Linaclotide at 0.0625–0.5 mg daily for 12 weeks significantly improved global symptom relief compared with placebo (23.2% vs. 34.8–38.7%), with the 0.5 mg dose also superior for CSBM, SBM, and abdominal pain (46). These findings suggest that higher doses may be more effective in Japanese patients.

### Efficacy on symptoms and QoL

Although Phase II studies provided valuable preliminary insights into the efficacy of linaclotide, its effects on symptom relief and quality of life (QoL) were confirmed in a series of Phase III trials conducted across North America, China, Japan, and Oceania, encompassing diverse patient populations.

#### *Efficacy in Western Populations*

Evidence from Western populations is derived mainly from two pivotal randomized, placebo-controlled Phase III trials conducted in North America, which supported FDA approval of linaclotide (47–48). Across 118 centers, 800 and 804 patients meeting Rome II IBS-C criteria received oral linaclotide 290  $\mu\text{g}$  once daily for 12 and 26 weeks, respectively. The 12-week study included a 4-week randomized withdrawal phase to assess symptom recurrence.

Both trials applied FDA-defined responder criteria, requiring for at least 6 of 12 weeks: (1)  $\geq 30\%$  reduction in mean daily worst abdominal pain and (2)  $\geq 1$  additional complete spontaneous bowel movement (CSBM) per week (49–50). Secondary outcomes included abdominal discomfort, bloating, stool frequency and consistency, and straining.

In the 12-week study, 33.6% of linaclotide-treated patients met the FDA endpoint versus 21% with placebo (NNT = 8.2). Bowel improvements appeared within four weeks, while pain relief followed by week six.

Table 2. — Summary of randomized clinical trials (RCT) on the use of linaclotide in the management of constipation-predominant Irritable Bowel Syndrome (IBS-C).

Reference	Phase	Linaclotide dose (µg)	Duration	N	Study endpoints
Andresen (2007) [44]		100, 1000		36	Effect on stool frequency, stool consistency, ease of passage, and time to first bowel movement
Johnston (2010) [45]	IIb	75, 150, 300, or 600	12 weeks	420	Effect on bowel habits and abdominal symptoms Improvement from 1 <sup>st</sup> week Frequency of adverse events
Chey (2012) [48]	III	290	26 weeks	804	Effect on abdominal and bowel symptoms Frequency of adverse events
Rao (2012) [47]	III	290	12 weeks followed by a 4-week withdrawal period	800	Effect on abdominal pain and bowel symptoms Frequency of adverse events
Quigley (2013) [51]	III	290	1 <sup>st</sup> trial: 12 weeks 2 <sup>nd</sup> trial: 26 weeks	1608	12-week improvement in abdominal pain/discomfort and degree-of-relief Sustainment of response beyond the 12 weeks
Lacy (2014) [56]	Pooled analysis (2 phase III trials)	290	12 weeks	1602	Improvement or somewhat relief in abdominal pain, stool frequency, global IBS symptoms and treatment satisfaction
Rao (2014) [53]	Pooled analysis (2 phase III trials)	290	12 weeks	1602	Improvement in bloating, fullness, discomfort and pain Frequency of adverse events
Buono (2014) [64]	Post-hoc (2 phase III trials)	290	12-26 weeks	1602	In 12 weeks: Impact on presenteeism, overall work productivity loss, and daily activity impairment In 26 weeks: Impact on the same variables Total annual income preservation per employer
Camilleri (2015) [58]	Pooled analysis (2 phase III trials)				Determination of clinically meaningful improvement in abdominal pain, discomfort, spontaneous bowel movements based on agreement with FDA/EMA endpoints
Fukudo (2018) [46]	Phase II dose finding trial	62.5, 125, 250, or 500	12 weeks	559	Determination of the minimal dose that improves IBS symptoms with smallest frequency of adverse events
Yang (2018) [59]	III	290	12 weeks	839	Improvement in abdominal pain/discomfort and degree of relief, spontaneous bowel movement/complete spontaneous bowel movement frequency, stool consistency, straining, abdominal pain, abdominal discomfort, and abdominal bloating. Frequency of adverse events and discontinuation rate
Fukudo (2018) [61]	III, OLE		12-40 weeks	500 OLE: 324	Global improvement and improvement in complete spontaneous bowel movements, and abdominal pain/discomfort at 12 weeks. Improvement rate up to 40 weeks Safety data up to 40 weeks

Farmer AD (2019) [42]		290	28 days		Effect on intestinal pH, colonic transit time, gastric emptying or small bowel transit. Correlation among improvement in motility and symptom intensity, unpleasantness, and visceral sensitivity.
Serrano-Falcón B (2019) [63]	IIIb	290	12 weeks	96	Time to clinical response in digestive non-intestinal and extra-digestive symptoms between 4 and 12 weeks Frequency and severity of adverse events
Rao SSC (2020) [43]		290		39	Effect on afferent gut-brain signalling Effect on abdominal symptoms and quality of life
Chey WD (2021) [71]		Delayed release			Effect of alterations in the site of drug delivery in the intestine on abdominal pain and bowel habits so as to expand the use of linaclotide in the other IBS subtypes
Chang L (2021) [57]	IIIb	290	12 weeks	614	Effect on multiple abdominal symptoms important to patients with IBS-C (bloating, discomfort, and pain) using a novel scoring system deriving from the Diary for IBS Symptoms-Constipation
Peng LH (2022) [60]	III	290	12 weeks		Effect and tolerance in Chinese patients with IBS-C patients Time to onset of response
Brenner DM (2022) [	post hoc	290	12 weeks	2350	Improvement in bowel symptoms Time of onset of symptomatic improvement Comparison between early and late responders

During withdrawal, symptoms recurred in those switched to placebo. Diarrhea was the main adverse event (5.7%), usually mild and early in treatment (47).

In the 26-week study, 33.7% of patients on linaclotide met the endpoint compared with 13.9% on placebo (NNT = 5.2), with consistent benefits across all secondary measures. Diarrhea remained the predominant, generally mild, adverse effect, leading to discontinuation in 4% (48).

For the EMA submission, responder definitions were adjusted to emphasize abdominal pain/discomfort and global IBS relief (51–52). Linaclotide achieved significantly higher response rates for both measures in the 12- and 26-week trials (pain/discomfort: 54.8% vs 41.8% and 54.1% vs 38.5%; global relief: 37% vs 18.5% and 39.4% vs 16.6%). Benefits extended to bloating and quality of life, particularly in patients with severe IBS-C (51–53).

Meta-analyses confirmed moderate efficacy across FDA and EMA endpoints and significant QoL improvements (54–55). Lacy et al. reanalysis of 1,602 participants showed that over 60% of “non-responders” still experienced meaningful symptom relief and treatment satisfaction, suggesting that stringent regulatory criteria may underestimate linaclotide’s clinical benefit (56–58).

*Efficacy in Other Populations*

The efficacy of linaclotide has also been demonstrated in two Phase III programs conducted in Asia for regional approval in China and Japan.

In China, a multicenter, randomized, double-blind, placebo-controlled 12-week trial across 98 sites in China, North America, and Oceania enrolled 839 patients meeting Rome III IBS-C criteria. Participants received linaclotide 290 µg or placebo once daily and recorded symptoms electronically. Co-primary endpoints, based on EMA criteria, were abdominal pain/discomfort and global IBS symptom relief. Linaclotide significantly outperformed placebo for both: 60.0% vs 48.8% achieved pain/discomfort response (P = 0.0010; OR 1.59; 95% CI 1.21–2.09; NNT = 8.9), and 31.7% vs 15.4% achieved global relief (P < 0.0001; OR 2.56; 95% CI 1.83–3.58; NNT = 6.1). Improvements appeared within one week and persisted through week 12. Results were consistent across regions, with diarrhea being the most common adverse event (< 1% discontinuations) (59–60).

In Japan, a randomized, double-blind, placebo-controlled study with a 40-week open-label extension evaluated 500 patients from 60 centers. Participants received linaclotide 0.5 µg or placebo for 12 weeks, followed by open-label treatment with optional dose reduction to 0.25 µg. Linaclotide significantly improved global IBS symptoms and CSBM responder rates versus placebo (P < 0.05). During the extension, 8% required dose reduction, and no re-escalation was needed. Patients switching from placebo achieved comparable outcomes. Diarrhea remained the most frequent adverse event (61).

*Efficacy in Work Productivity and Daily Activities*

A post hoc analysis of two pivotal North American

Table 3. — Summary of real-world evidence on the use of linaclotide in the management of constipation-predominant Irritable Bowel Syndrome (IBS-C).

Reference	Design	Study outcomes	Participants	Key conclusions
Shearer J (2018) [72]	Rome III/United Kingdom	Efficacy endpoint: Improvement in IBS-SSS >75 at 4 weeks	108	At 4 weeks <input type="checkbox"/> 43.5% discontinuation due to lack of efficacy or being lost to follow-up or due to adverse events. <input type="checkbox"/> 39.8% adverse events mainly diarrhea (25.9%) and abdominal pain (5.6%)
Geijo Martínez F (2018) [74]	Prospective single-center	Efficacy endpoint: Number of bowel movements per week Secondary endpoints: Treatment satisfaction Changes in the frequency and severity of abdominal pain and bloating	30 females	After 18 months of follow-up: <input type="checkbox"/> Significant improvement in the number of weekly bowel movements from 0.9 to 4.7 <input type="checkbox"/> Significant improvement in abdominal pain and bloating <input type="checkbox"/> Significant treatment satisfaction
Andresen V (2018) [75]	Prospective Germany	Efficacy endpoints: Severity of abdominal pain and bloating Frequency of bowel movements Safety endpoints: Treatment-related adverse events	375	At 52 weeks <input type="checkbox"/> Significant improvement in abdominal pain mean intensity (4.87 vs 2.40), bloating mean intensity (5.30 vs. 2.86), and mean bowel movement frequency (2.71 vs. 4.38). <input type="checkbox"/> 5% developed diarrhea
Yiannakou Y (2018) [73]	1-year, multicentre, prospective, United Kingdom	Efficacy endpoints: Change from baseline in IBS-SSS at 12 & 52 weeks Safety endpoints: Adverse events were recorded	202 185 females	At 12 & 52 weeks: <input type="checkbox"/> Significant decrease in IBS-SSS from baseline <input type="checkbox"/> 38.1% adverse events 26.7% diarrhea 10.4 % abdominal pain 6.4% abdominal distension
Mascarenhas-Saraiva MJ (2019) [76]	prospective single-center study Rome IV criteria.	Efficacy endpoints: abdominal pain and bloating number of bowel movements Treatment satisfaction Safety endpoints: Frequency of adverse events	40	Between baseline and 6 months <input type="checkbox"/> Significant reduction in pain (93% vs 33%) and bloating (93% vs 20%) <input type="checkbox"/> Significant increase in weekly bowel movements <input type="checkbox"/> 97% treatment satisfaction <input type="checkbox"/> 10% diarrhea (67% mild)
Taylor DCA (2019) [79]		Impact of stool consistency on patient-reported bowel movement satisfaction		<input type="checkbox"/> LoWS or intermediate were satisfactory <input type="checkbox"/> Linaclotide users were more satisfied than controls
Pohl D (2019) [77]	Multicentre (31 primary, secondary, and tertiary centers in Austria and Switzerland)	Efficacy endpoints: Severity of abdominal pain and bloating Frequency of bowel movements Physicians' global assessment Safety endpoints: Treatment-related adverse events Duration: 4 weeks Austria 16 weeks Switzerland	128 >75% females	Between baseline and 4 weeks: <input type="checkbox"/> Significant reduction in pain (5.8 to 2.7) and bloating (5.8 to 3.1) <input type="checkbox"/> Significant increase in mean bowel movements frequency (2.1 to 4.5) <input type="checkbox"/> Good effectiveness in >70% of patients according to physicians <input type="checkbox"/> 7-15 % diarrhea

Shah ED (2020) [80]	University of Michigan Electronic Patient Record	reasons and timing of discontinuation of linacotide vs lubiprostone	1,612	<ul style="list-style-type: none"> <li>☐ Lower risk of discontinuation for linacotide (hazard ratio: 0.6, 95% confidence interval [CI] 0.5-0.8)</li> <li>☐ Discontinuation rates for linacotide: 3mo: 14% &amp; 12mo:24%</li> <li>☐ Loss of prescription coverage and Intolerance were the main reasons for discontinuation</li> </ul>
Shah ED (2022) [81]	Cohort Analysis at an Integrated Healthcare System (Michigan Medicine healthcare)	Impact of chronic overlapping pain conditions, mood disorders, or concurrent medications on the risk of discontinuing linacotide or lubiprostone  Follow-up duration : 2 years	225 patients on linacotide 492 patients on lubiprostone 86.9% females	<ul style="list-style-type: none"> <li>☐ Patients with COPC (HR = 0.566; 95%CI = 0.371-0.863) and females (HR = 0.535; 95%CI = 0.307-0.934) had a lower risk of discontinuing linacotide</li> <li>☐ COPCs and sex appear to influence the likelihood of discontinuation of linacotide</li> <li>☐ Routine assessment for comorbid COPCs prior to initiating therapy may optimize IBS-C treatment selection and outcomes in practice</li> </ul>
Liu L (2022) [78]	prospective multicentre (10 primary institutions)	Efficacy endpoints: Changes in defecation, abdominal symptoms, IBS-SSS, IBS-QOL, Zung Self-Rating Anxiety Scale and Self-Rating Depression Scale Safety endpoints: Adverse events frequency	97 patients 56.7% females	<ul style="list-style-type: none"> <li>☐ From baseline to 4 &amp; 12 weeks: Significant increase in the number of the patients' defecation per week and Bristol stool form scale scores</li> <li>☐ Significant reduction in IBS-SSS</li> <li>☐ Significant improvement in quality of life                             <ul style="list-style-type: none"> <li>☐ Treatment satisfaction 4 weeks: 79% 12 weeks: 100%</li> </ul> </li> <li>☐ Adverse events: 11% diarrhea</li> </ul>

Phase III trials evaluated linacotide’s effect on work productivity using the WPAI:IBS-C questionnaire. Among 1,602 participants (71.7% employed), linacotide significantly improved presenteeism, work productivity loss, and activity impairment at week 12 (reductions of 5.2%, 6.1%, and 4.7%, respectively; all  $P < .01$ ), with similar results at week 26. Productivity gains equated to 103–156 work hours annually, corresponding to avoided indirect costs of USD \$3,209–\$4,861 per employed patient (62).

**Predictors of Response**

Predictive factors were assessed in an open-label Phase IIIb study across 12 Spanish hospitals, enrolling 96 patients with moderate-to-severe IBS-C (IBS-SSS  $\geq 175$ ). Participants received linacotide 290  $\mu$ g daily for 12 weeks. Clinical response—defined as  $> 30\%$  IBS-SSS reduction or  $< 75$  points plus patient-reported improvement—was achieved by 25.0% and 36.7% of patients at week 12 in the ITT and per-protocol analyses. Diarrhea (35.4%) was the most frequent adverse event. Early improvement at week 4 predicted sustained response at week 12 (OR 6.5; 95% CI 2.1–19.8), suggesting early symptom relief as a marker of long-term benefit (63).

**Safety and tolerability**

Regarding safety and tolerability, throughout the abovementioned market-authorizing trials of linacotide was found to be well-tolerated with its most common side effects involving the gastrointestinal system, being dose-dependent and relating to its mechanism of action. Available evidence showed that diarrhea was the most common side effect, occurring in approximately 20 % of patients receiving linacotide and leading to significantly more discontinuations than placebo. (RR, 14.94; 95% CI, 4.65–48.03). Diarrhea often started within the first two weeks of the onset of treatment and was more profuse in those patients receiving larger dosages. Other common side effects were abdominal pain, flatulence, abdominal distension, urgency, fecal incontinence, viral gastroenteritis, and headache. No serious adverse events were recorded with two ischemic colitis cases and 3 deaths being all unrelated to linacotide. (64).

**Comparative efficacy among available treatments for IBS-C**

Over the past two decades, several pharmacologic agents besides linacotide have been approved for the

treatment of IBS-C, targeting intestinal secretion and visceral hypersensitivity. However, their comparative efficacy remains uncertain, as no head-to-head randomized controlled trials have been performed, limiting clinicians' ability to determine optimal treatment sequencing.

To address this, data from meta-analyses and network meta-analyses have been used to guide therapeutic decisions. These studies consistently identify linaclotide (290 µg once daily) as the most effective agent for improving abdominal pain, bloating, and complete spontaneous bowel movement (CSBM) frequency. Diarrhea was the most common adverse event across all therapies evaluated (65–68).

### Cost-Effectiveness of Available Therapies

Direct comparative studies on the cost-effectiveness of IBS-C treatments are lacking, but two economic evaluations offer important insights. Shah et al. performed the first comprehensive analysis incorporating pharmacologic, dietary, and psychological interventions for IBS (69–70). Using a decision-analytic model with a one-year time horizon, and cost inputs from national healthcare databases, the study assessed outcomes from both payer and patient perspectives. From the payer standpoint, non-pharmacologic strategies—such as the low-FODMAP diet, cognitive behavioral therapy, and neuromodulation—were less costly than prescription medications, with drug pricing and management costs of untreated IBS-C being major determinants of value. From the patient perspective, linaclotide emerged as both the most effective and least costly pharmacologic option, supporting its use as a first-line therapy (70).

### Advancements in Linaclotide Formulation and Delivery

Across Phase I–III trials, linaclotide has consistently reduced abdominal pain and enhanced intestinal secretion, with diarrhea as its principal dose-dependent adverse effect. Because its primary action occurs in the proximal small intestine—the main site of secretion and absorption—modifying the site of drug release has been explored to improve tolerability without reducing efficacy. Two delayed-release (DR) formulations were developed: DR1, designed for ileal release, and DR2 (MD-7246), targeted to the cecum. In a 12-week, randomized, dose-ranging Phase IIb trial including 532 patients with IBS-C, DR1 provided no added benefit over standard linaclotide, whereas DR2 significantly reduced abdominal pain with minimal changes in bowel frequency. These findings suggest that site-specific delivery may separate linaclotide's secretory and analgesic effects, potentially extending its use to other IBS subtypes (71).

### Insights from Real-World Studies

While clinical trials have established linaclotide's efficacy and safety, their results are limited by selective populations and short follow-up. Real-world evidence (RWE) complements these findings by assessing broader, unselected cohorts and clarifying linaclotide's role in routine IBS-C management, with most data derived from European studies using Rome III or IV criteria (72–78).

#### United Kingdom Studies

The first real-world study by Shearer et al. included 108 patients with Rome III IBS-C treated with linaclotide 290 µg daily for four weeks (72). A  $\geq 75$ -point IBS-SSS reduction defined response, achieved by 45.4% of patients. Significant improvements occurred in straining (3.9 → 2.0;  $P < .001$ ) and stool frequency (3.8 → 8.9;  $P < .001$ ). Adverse events occurred in 39.8%—mainly diarrhea (25.9%)—leading to discontinuation in 43.5%.

A subsequent 52-week multicenter UK study of 202 patients (66.8% severe IBS-C) reported response rates of 55.6% and 53.9% at weeks 12 and 52, with mean IBS-SSS reductions of  $-77.0$  and  $-70.7$  ( $P < .001$ ) (73). Adverse events were noted in 38.1%—mainly diarrhea (26.7%)—resulting in discontinuation in 25.2%, mostly within the first three weeks.

Collectively, UK studies confirmed linaclotide's real-world efficacy but observed higher discontinuation rates than pivotal trials. Later European studies demonstrated comparable effectiveness with improved tolerability (74–77).

#### Evidence from Asia

Liu et al. conducted a 12-week prospective study in China involving 97 Rome IV IBS-C patients from 10 centers (78). Linaclotide 290 µg daily significantly improved abdominal symptoms, defecation frequency, stool consistency, and psychological well-being ( $P < 0.05$  for all). Diarrhea occurred in 11.6% of patients. Early discontinuation was 40.2%, though nearly half stopped due to symptom resolution rather than intolerance. This study was the first to document linaclotide's beneficial effects on anxiety and depression in IBS-C.

### Patients' and physicians satisfaction

Real-world studies have provided valuable insights into patient and physician satisfaction with linaclotide for IBS-C. High satisfaction rates reported in clinical trials have been confirmed in observational studies from Europe and China (74,76,78). Across these cohorts, over 70% of patients expressed satisfaction, reflecting strong acceptance in everyday practice.

Unlike clinical trials, where satisfaction plateaued early, real-world studies showed progressive improvement—nearly all patients continuing treatment beyond 12 weeks

reported satisfaction, while most dissatisfaction occurred within the first two weeks, likely due to early variability in response and tolerance (76,78).

Symptom relief and stool consistency were key determinants of satisfaction. In a Spanish study, Geijo Martínez et al. found that improvement in abdominal pain, discomfort, and bowel frequency strongly correlated with satisfaction (74). Similarly, analysis from the CONTOR registry ( $n = 1,806$ ) showed higher satisfaction among those with intermediate or loose stools versus hard stools (61.2% and 51.2% vs 19.4%) (79).

Physician satisfaction was also high. A multicenter study in Austria and Switzerland involving 138 patients reported “good” to “moderate” satisfaction (mean scores 2.9 and 4.6, respectively), with over 70% rating efficacy as good or excellent (77). Comparable findings from Germany confirmed consistent approval and tolerability (75). Regionally, Austrian physicians (60.5%) prescribed linaclotide as a novel option, while in Switzerland and Germany it was mainly used after failure of previous therapies. Poor tolerability of prior agents was rarely cited, reinforcing linaclotide’s status as an effective, well-accepted treatment in clinical practice (75,77).

### Predictors of treatment discontinuation

Real-world studies have shown variable discontinuation rates for linaclotide across UK, non-UK, and clinical trial settings, largely attributed to broader inclusion criteria and patient heterogeneity. Identifying predictors of discontinuation remains clinically relevant for optimizing treatment adherence.

In a retrospective analysis of 1,612 patients from the University of Michigan Electronic Medical Record, Shah et al. found that linaclotide users had a lower discontinuation risk than lubiprostone users (HR = 0.6; 95% CI, 0.5–0.8), with 3- and 12-month discontinuation rates of 14% and 24% versus 23% and 43%, respectively (80). Intolerance accounted for over half of discontinuations (HR = 1.6; 95% CI, 1.2–2.3), while treatment insufficiency was less common (HR = 0.5; 95% CI, 0.4–0.8).

A subsequent cohort study within the Michigan Medicine network (225 linaclotide, 492 lubiprostone users) reported that female sex (HR = 0.535; 95% CI, 0.307–0.934) and chronic overlapping pain conditions (HR = 0.566; 95% CI, 0.371–0.863) were linked to lower discontinuation risk (81). No associations were observed with age, mood disorders, or opioid/benzodiazepine use. Overall, linaclotide was well tolerated, with discontinuation primarily due to mild intolerance rather than inefficacy, and better persistence among women and those with pain comorbidities.

### Efficacy and safety in special populations

The pivotal linaclotide trials excluded children, pregnant women, and elderly patients; however, real-

world studies have provided insight into its use in these groups (82–84).

#### *Pediatric Populations*

Baaleman et al. conducted a retrospective review at Nationwide Children’s Hospital (Ohio) including 93 patients under 18 years, 33 with IBS-C (82). The cohort was predominantly female with a median age of 15 years. Among IBS-C patients, 42% achieved a clinical response within two months. Reported adverse events—diarrhea, abdominal pain, nausea, and bloating—were consistent with adult data.

#### *Elderly Populations*

At Sapporo Medical University Hospital, 52 patients treated with linaclotide were analyzed by age (<65 vs  $\geq 65$  years) and dose (0.25 or 0.5 mg/day) (83). Sixty percent were aged  $\geq 65$  years. Diarrhea was the most common adverse event (64.5% vs 42.9%,  $P = 0.130$ ), with no age-related difference in efficacy. Risk factors for diarrhea included use of constipation-inducing medications (OR 5.79;  $P = 0.047$ ) and linaclotide monotherapy (OR 11.1;  $P = 0.040$ ).

#### *Pregnancy and Lactation*

Although no studies have examined linaclotide use during pregnancy, a multicenter pharmacokinetic study in seven lactating women found no detectable concentrations of linaclotide or its active metabolite in breast milk (<0.25  $\mu\text{g/L}$  and <1  $\mu\text{g/L}$ , respectively), indicating minimal or no transfer (84).

### Cost-effectiveness

Following linaclotide’s introduction, the overall cost of IBS-C management has risen due to new pharmacologic options; however, its superior efficacy and quality-of-life benefits may offset this increase. Real-world economic evaluations from the United States, Scotland, and China have examined its cost-effectiveness compared with standard therapies.

In China, a Markov model compared linaclotide, polyethylene glycol, and lactulose over one year (86). Quality-adjusted life years (QALYs) were 0.821, 0.795, and 0.781, respectively, with total costs of USD 1,120, 1,276, and 1,375. Linaclotide provided higher QALYs at a lower overall cost, confirming its cost-effectiveness within the Chinese healthcare setting.

Similarly, a Scottish National Health Service (NHS) evaluation used a 5-year Markov model to compare linaclotide with antispasmodics and antidepressants (87). Linaclotide produced incremental costs of £659 and 0.089 additional QALYs, yielding an ICER of £7,370 per QALY versus antidepressants. The probability of cost-effectiveness at a £20,000 per

QALY threshold was 73%, demonstrating favorable economic value.

In a retrospective U.S. study, Taylor et al. found that linaclotide use significantly reduced healthcare resource utilization, including outpatient visits and hospitalizations, resulting in substantial cost savings (88).

Collectively, these real-world analyses indicate that linaclotide is a cost-effective option for IBS-C management across diverse healthcare systems, with its higher upfront costs balanced by improved outcomes and reduced long-term healthcare use.

### Limitations

The available real-world evidence (RWE) is heterogeneous, with differences in inclusion criteria, clinical severity, and diagnostic frameworks (Rome II vs III vs IV), which limits direct comparability with pivotal Phase III trials and across regions (72–78). Observational designs introduce selection bias, and higher discontinuation rates in UK cohorts likely reflect broader, less selected populations. Predictors of sustained benefit (e.g. early symptom improvement) and predictors of discontinuation (e.g. intolerance vs inefficacy, sex differences) require further validation (63,80–81). Finally, although both randomized trials and RWE consistently support linaclotide's clinical value, its precise position in IBS-C treatment algorithms remains to be defined in the absence of head-to-head comparative trials.

### Potential place in the pharmacotherapy and Future Directions

Linaclotide is the first orally administered guanylate cyclase-C (GC-C) agonist approved by major regulatory authorities for the treatment of adults with IBS-C. The American College of Gastroenterology recommends its use, though its exact placement within treatment algorithms continues to evolve. Clinical trials have established its efficacy, safety, and mechanism of action, while real-world evidence (RWE) has confirmed its effectiveness and tolerability in routine practice. Collectively, these findings support linaclotide as a first-line therapeutic option for IBS-C, with network meta-analyses demonstrating superiority over other available agents.

Although linaclotide has a higher acquisition cost than conventional therapies, its broader benefits—such as sustained symptom relief, improved quality of life, and potential long-term healthcare savings—justify its early use. Diarrhea remains the most common but generally mild adverse event. Response does not appear to be influenced by age, comorbidities, or concomitant medications, though male sex has been associated with slightly higher discontinuation rates. Further data are needed to guide use in children, pregnant women, and the elderly, who are often excluded from clinical trials.

Future research should focus on head-to-head randomized controlled trials to clarify comparative efficacy and refine treatment algorithms. Expanded RWE in diverse and underrepresented populations will also be critical to confirming linaclotide's safety, cost-effectiveness, and optimal positioning within the growing pharmacologic landscape for IBS-C.

### Conclusion

Linaclotide is a safe and effective therapy for irritable bowel syndrome with constipation (IBS-C), supported by robust evidence from randomized trials and real-world studies. By activating guanylate cyclase-C (GC-C) receptors on intestinal epithelial cells, it increases cyclic guanosine monophosphate (cGMP), enhances secretion and motility, and reduces visceral pain.

Clinical trials across North America, Japan, and China consistently demonstrate significant improvements in complete spontaneous bowel movements (CSBMs), abdominal pain, bloating, and quality of life (QoL), with benefits evident within the first week and sustained throughout treatment. Real-world data corroborate these results, showing gains in productivity, psychological well-being, and satisfaction, though with higher discontinuation rates—mainly due to mild-to-moderate diarrhea.

Linaclotide demonstrates favorable outcomes in varied populations, including the elderly and children, while data in pregnancy and lactation remain limited. Early response predicts long-term benefit, and male sex may slightly increase discontinuation risk. Network meta-analyses confirm its superiority in reducing abdominal pain and bloating, and economic evaluations from multiple regions establish its cost-effectiveness.

Although endorsed by the American College of Gastroenterology, linaclotide's precise position within treatment algorithms requires further clarification. Future research should focus on direct comparative trials and expanded real-world evidence in underrepresented groups. Overall, linaclotide is a well-tolerated, efficacious, and cost-effective therapy that meaningfully improves patient outcomes, solidifying its role as a cornerstone in IBS-C management.

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