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Efficacy and safety of linaclotide for opioid-induced constipation in patients with chronic noncancer pain syndromes from a phase 2 randomized study

Darren M. Brenner[a,*], Charles E. Argoff[b], Susan M. Fox[c], Wieslaw Bochenek[c], Patricia D'Astoli[c], Rick E. Blakesley[d], David S. Reasner[e], Christopher R. O'Dea[f], Brooks D. Cash[g]

Abstract

Constipation is the most common adverse event (AE) of opioid therapy. This multicenter, phase 2 study evaluated the efficacy and safety of linaclotide in treating opioid-induced constipation (OIC) in patients with chronic noncancer pain syndromes (NCT02270983). Adults with OIC ($<$3 spontaneous bowel movements [SBMs]/week) related to chronic noncancer pain were randomized 1:1:1 to receive linaclotide 145 μg, linaclotide 290 μg, or placebo once daily for 8 weeks. The primary endpoint was change from baseline in 8-week SBM frequency rate (SBMs/week). Secondary efficacy endpoints included 6/8-week SBM 3 + 1 responders, time to first SBM, and changes from baseline in 8-week stool consistency, abdominal bloating, and straining. Additional endpoints included treatment satisfaction and adequate relief responders. In total, 254 patients were randomized: 87, 88, and 79 received linaclotide 145 μg, linaclotide 290 μg, and placebo, respectively. The mean changes from baseline in SBMs/week during the treatment period were 2.9 and 3.5 in the linaclotide 145 and 290 μg groups ($P < 0.01$ for both doses), respectively, vs 1.6 in the placebo group. Diarrhea, the most common AE, was generally mild, resulting in 1.1%, 5.7%, and 1.3% of patients discontinuing in the linaclotide 145 μg, linaclotide 290 μg, and placebo groups, respectively. No serious AEs related to diarrhea were reported in any treatment group. Compared with placebo, linaclotide-treated patients had significant improvements in stool consistency, straining, abdominal bloating, and treatment satisfaction scores ($P < 0.05$). Linaclotide significantly improved OIC symptoms and was well tolerated in patients with chronic noncancer pain.

Keywords: Bowel movement, Guanylate cyclase-C agonist, Opioid use, Opioid constipation

1. Introduction

Opioids are important for the management of various cancer- and non–cancer-related acute and chronic pain conditions. In 2017, over 190 million opioid prescriptions were dispensed by retail pharmacies, with a prescribing rate of 58.5 per 100 people.[12] Opioid-induced constipation (OIC) is the most common side effect associated with chronic opioid use,[36] with a prevalence rate of 41% to 81% in patients with chronic noncancer pain syndromes.[4,24]

Although opioids reduce pain by binding to and activating μ-opioid receptors in the central nervous system,[35] they also activate μ-opioid receptors in neurons in the peripheral nervous system and the gastrointestinal (GI) tract epithelium, leading to opioid-related GI side effects including nausea, constipation, and bowel dysfunction.[10,21,39] Through binding to μ-opioid receptors, opioids inhibit release of various neurotransmitters such as acetylcholine, which prevents water and electrolyte movement into the GI tract, resulting in slower intestinal transit.[8,36] Opioid-induced constipation symptoms include sensation of incomplete evacuation, lumpy/hard stools, excessive straining, and decreased defecation frequency.[6,26,43] Importantly, although tolerance develops for many non-GI opioid-related side effects, it does not develop for OIC, resulting in persistent bothersome symptoms.[24,31]

Prophylactic treatment, including increased fluid and fiber intake and osmotic and stimulant laxatives, is recommended for OIC patients.[31] Recent guidelines recommend prescription treatment for OIC if there is insufficient clinical benefit observed with non-prescription therapies. These guidelines also recommend using the Bowel Function Index, a 0 to 100 numerical analog scale including 3 variables: ease of defecation, feeling of incomplete bowel evacuation, and personal judgment of constipation.[2] Although the Bowel Function Index may be useful for characterizing OIC severity and need for prescription therapy, it is not diagnostic for OIC and not

widely used in routine clinical practice. Currently, 3 peripherally acting μ-opioid receptor antagonists are approved by U.S. Food and Drug Administration (FDA) for treating OIC due to chronic opioid use for noncancer pain: methylnaltrexone (Salix Pharmaceuticals, Inc, Bridgewater Township, NJ), naloxegol (AstraZeneca Pharmaceuticals, UK/Daiichi-Sankyo, Japan), and naldemedine (Shionogi Inc, Japan and Purdue Pharma LP, Stamford, CT).[43] Lubiprostone (Takeda Pharmaceuticals, Inc, Tokyo, Japan), a type-2 chloride channel and cystic fibrosis transmembrane conductance regulator activator also approved for this condition, facilitates an increase in intestinal fluid secretion and gut motility; however, it may have limited efficacy in OIC patients taking diphenylheptane opioids (eg, methadone).[9,37]

Linaclotide (Allergan plc, Madison, NJ and Ironwood Pharmaceuticals, Inc, Boston, MA), a minimally absorbed 14-amino-acid peptide guanylate cyclase-C agonist, is an FDA-approved treatment for irritable bowel syndrome with constipation (IBS-C) (290 μg) and chronic idiopathic constipation (CIC) (145 and 72 μg).[7,40,41] Guanylate cyclase-C activation increases intracellular and extracellular concentrations of cyclic guanosine monophosphate, resulting in chloride and bicarbonate secretion into the intestinal lumen, leading to elevated intestinal fluid and transit. Moreover, increased extracellular cyclic guanosine monophosphate has been shown in animal models to decrease pain-sensing nerve activity; this is thought to be the mechanism yielding improved abdominal pain.[11,20,34] Thus, it is hypothesized that linaclotide may potentially reverse the deleterious effects of opioids on GI secretion, motility, and attendant symptoms of constipation. This study evaluated linaclotide's safety and efficacy for the treatment of OIC in adults receiving stable opioid treatment for chronic noncancer pain syndromes.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled, phase 2 study of linaclotide, conducted in 71 centers across the United States between October 2014 and August 2015 (ClinicalTrials.gov: NCT02270983). The study included screening and pretreatment periods (during which no study drug was administered), and a treatment period. The screening period of up to 28 days evaluated patient eligibility for the pretreatment period based on results of physical examination, medication history, medical/surgical history, laboratory tests, electrocardiogram, and colonoscopy (if applicable), and allowed for washout of prohibited medications (eg, opioid antagonists and lubiprostone). Patients who successfully completed screening assessments began the 2-week pretreatment period and used an interactive voice response system to complete daily and weekly OIC symptom assessments to ensure compliance with study procedures to be used during the treatment period, and to establish baseline values. Patients who successfully completed the pretreatment period were eligible for the 8-week treatment period (Supplementary Fig. 1, available at http://links.lww.com/PAIN/A914). Any over-the-counter or prescription laxatives, suppositories, or enemas used to treat OIC were not to be taken beginning the calendar day before the start of pretreatment (pretreatment visit). At the pretreatment visit, patients chose bisacodyl 5 mg tablets or 10 mg suppositories as rescue medication. Rescue medication was made available to patients throughout the pretreatment and treatment periods, and was to be used if more than 72 hours had passed since the patient's last bowel movement or if symptoms became intolerable.

At the start of the treatment period, eligible patients were randomized 1:1:1 to receive either linaclotide 145 μg/day, linaclotide 290 μg/day, or placebo in a single dose 30 minutes before breakfast. Treatment was assigned through codes generated by a statistical program at Allergan plc and implemented by an interactive web response system that the study centers accessed. The study protocol was approved by the institutional review board or independent ethics committee for each study center. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and complied with Good Clinical Practice and International Conference on Harmonisation guidelines. All authors had access to the study data and reviewed and approved the final manuscript.

2.2. Patients

Eligible patients were aged 18 years or older with chronic noncancer pain for ≥3 months requiring treatment with an opioid analgesic for ≥4 days per week for ≥8 weeks before the screening visit. Participants self-administered a stable dose of a full opioid agonist (minimum total daily dose equianalgesic to oral morphine 30 mg) with the expectation that they would continue this regimen for the study duration. In addition, bowel symptom criteria based on the Rome III definition for CIC required that patients have <3 spontaneous bowel movements (SBMs) per week for ≥4 weeks before screening, with >25% of those BMs accompanied by ≥1 other constipation symptom (straining, lumpy or hard stools, and/or sensation of incomplete evacuation).[17]

Key exclusion criteria included: use of opioids for abdominal pain or for a condition that had GI manifestations that could confound the interpretation of the study results; loose or watery stools (Bristol Stool Form Scale [BSFS] score of 6 or 7) in the absence of any laxative, suppository, or enema for >25% of BMs during the 3 months before the study; and a history or diagnosis of diabetic neuropathy or other overlapping GI conditions (IBS, chronic constipation before initiation of opioid treatment, diverticulitis, narcotic bowel syndrome, inflammatory bowel disease, ischemic colitis, active peptic ulcer disease, bowel obstruction, pseudo-obstruction, colonic inertia, megacolon, megarectum, descending perineum syndrome, solitary rectal ulcer syndrome, fecal impaction that required hospitalization, cathartic colon, laxative or enema abuse, or pelvic floor dysfunction). All patients provided written informed consent to participate in the trial.

2.3. Efficacy assessments

Patients completed daily and weekly assessments during the pretreatment and treatment periods by calling an interactive voice response system. Daily assessments included: occurrence of BMs; stool consistency of each BM measured using the BSFS (1 = separate hard lumps like nuts [difficult to pass]; 7 = watery, no solid pieces [entirely liquid])[29]; straining associated with each BM using a 5-point scale (1 = not at all; 5 = an extreme amount); abdominal bloating, pain at its worst, and discomfort assessed using separate 11-point scales (0 = none; 10 = very severe); any additional constipation medications used (Yes/No); and use of chosen rescue medication.

Weekly assessments included: OIC severity using a 5-point scale (1 = none; 5 = very severe); treatment satisfaction using a 5-point scale (1 = not at all satisfied; 5 = very satisfied); adequate relief (1 = Yes; 2 = No); and degree of relief of OIC symptoms using a 7-point scale (1 = completely relieved; 7 = as bad as I can imagine).

2.4. Efficacy endpoints

An SBM was defined as a BM that occurred in the absence of any laxative, enema, or suppository use during the calendar day of the BM or the calendar day before the BM. The primary efficacy endpoint was the change from baseline in 8-week SBM frequency rate (SBMs/week) during the treatment period. Secondary efficacy endpoints included proportion of 6-/8-week SBM 3 + 1 responders (defined as ≥3 SBMs/week plus an increase of ≥1 SBM/week from baseline for ≥6 out of 8 weeks), and changes from baseline in 8-week stool consistency, straining, abdominal bloating, and time to first SBM. A durable response characterized by 6-/8-week SBM 3 + 1 response also being achieved during 3 of the last 4 weeks of treatment (6-/8- + last 3-/4-week SBM 3 + 1 responders) was included as an additional endpoint. Other additional efficacy endpoints included weekly changes from baseline in SBM frequency rate, overall treatment satisfaction, changes from baseline in 8-week and weekly OIC severity, 6-/8-week adequate relief responder rate, and change from baseline in percent of days of rescue medication use.

2.5. Safety

Safety data collection included treatment-emergent adverse events (TEAEs), standard panel clinical chemistry, hematology and urinalysis (at screening, and at the day 1, week 4, and week 8 treatment period visits), vital signs (all visits), 12-lead electrocardiogram parameters (screening and week 8 visit), and changes in chronic pain that was managed with opioids assessed using the Brief Pain Inventory–Short Form (all visits). Reports of AEs, reported using the Medical Dictionary for Regulatory Activities version 18.0, were collected from patients throughout the study and at 30 days after treatment, and were summarized by treatment group (placebo, linaclotide 145 μg, and linaclotide 290 μg) and the overall linaclotide treatment group (combined linaclotide 145 and 290 μg).

2.6. Statistical analyses

This was the first linaclotide study in patients with OIC. By examining the estimates of change from baseline in 8-week SBM rate (the primary efficacy endpoint) from lubiprostone CIC and OIC studies,[16,18] and estimating the percent reduction in mean difference and SD estimates between indications, comparable linaclotide OIC estimates were projected using the linaclotide CIC phase 3 study data.[28] A sample size of 80 patients per treatment group was estimated to provide 59% to 89% power with α = 0.10 and a posterior probability that a population mean treatment difference was at least 0.9, being between 50% and 62%. Descriptive statistics were used to analyze baseline demographics and safety parameters. Continuous variables were summarized by number of patients, mean, SD, median, and minimum and maximum values. Categorical variables were summarized by number and percentage of patients. All efficacy analyses were based on the intent-to-treat population. This study was not designed to show statistically significant differences between linaclotide doses. All statistical tests were two-sided with no adjustment for multiplicity, and therefore P values are presented for descriptive purposes only. All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

For 8-week change from baseline, each linaclotide group was compared with the placebo group using an analysis of covariance model, with treatment group and geographic region as fixed-effect terms and the baseline value as a covariate. For weekly change from baseline, expressed using least squares mean, each linaclotide group was compared with the placebo group using a mixed-effects model for repeated measures, with treatment group, geographic region, visit, and treatment group-by-visit interaction as fixed-effect terms and the baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-patient results.

For responder rates, the proportion of responders in each linaclotide group was compared with the proportion in the placebo group using the Cochran–Mantel–Haenszel test controlling for geographic region. Patients with missing information were considered nonresponders. The time to first SBM distribution for each linaclotide group was compared with the placebo group using a log-rank test stratified by geographic region, and hazard ratios were estimated using a Cox proportional hazards regression model.

3. Results

3.1. Patient disposition, demographics, and baseline characteristics

Of the 674 screened patients, 418 entered the pretreatment period and 254 were randomized to linaclotide 145 μg/day (n = 87), linaclotide 290 μg/day (n = 88), or placebo (n = 79). Overall, 28 patients (11.0%) discontinued the study, most commonly due to AEs (n = 11) (Supplementary Fig. 2, available at http://links.lww.com/PAIN/A914). Two patients (1 each in the placebo and linaclotide 290 μg groups) were excluded from the safety and intent-to-treat populations as they did not receive treatment.

Demographic and baseline disease characteristics were similar between the 3 treatment groups (**Table 1**). The overall mean baseline SBM frequency rate across treatment groups was 1.07 SBMs/week, indicating severe OIC. The mean age was 53.2 years, with a high mean body mass index of 31.0 (range: 29.1-32.2) across treatment groups. Back pain (76.6%) and neck pain (11.9%) were the most common conditions necessitating chronic opioid use.

3.2. Primary efficacy endpoint

The change from baseline in 8-week SBM frequency rates (SBMs/week) was 2.9 and 3.5 in the linaclotide 145 and 290 μg groups, respectively, vs 1.6 in the placebo group (**Fig. 1**). The mean differences vs placebo were 1.3 (95% confidence interval [CI] 0.4-2.2; P = 0.0035) and 1.9 (95% CI 1.0-2.8; P < 0.0001) for the linaclotide 145 and 290 μg groups, respectively. Furthermore, for any level of improvement in the 8-week SBM frequency rate, a greater proportion of linaclotide-treated patients (both doses) achieved that level of improvement compared with placebo-treated patients (**Fig. 1B**).

3.3. Secondary efficacy endpoints

3.3.1. 6-/8-week SBM 3 + 1 responder rate

The 6-/8-week SBM 3 + 1 responder rates numerically favored linaclotide-treated patients, but the differences did not reach statistical significance. Overall, 40.2%, 47.1%, and 33.3% of patients receiving linaclotide 145 μg, linaclotide 290 μg, and placebo, respectively, achieved this endpoint (**Fig. 2A**). The odds of achieving this clinical

Table 1

Baseline demographics and disease characteristics.

Demographic parameter	Placebo (n = 78)	Linaclotide 145 μg (n = 87)	Linaclotide 290 μg (n = 87)	Total (N = 252)
Age, y, mean (SD)	52.2 (10.6)	53.1 (9.2)	54.0 (10.5)	53.2 (10.1)
≥65 y, n (%)	11 (14.1)	12 (13.8)	14 (16.1)	37 (14.7)
Female, n (%)	47 (60.3)	49 (56.3)	55 (63.2)	151 (59.9)
Race, n (%)				
White	66 (84.6)	71 (81.6)	72 (82.8)	209 (82.9)
African American	9 (11.5)	15 (17.2)	10 (11.5)	34 (13.5)
Asian	3 (3.8)	1 (1.1)	3 (3.4)	7 (2.8)
Other	0	0	2 (2.3)	2 (0.8)
Ethnicity, n (%)				
Hispanic or Latino	4 (5.1)	5 (5.7)	2 (2.3)	11 (4.4)
Not Hispanic or Latino	74 (94.9)	82 (94.3)	85 (97.7)	241 (95.6)
BMI (kg/m^2), mean (SD)	32.17 (8.57)	29.09 (6.32)	31.77 (7.39)	30.97 (7.54)
Morphine-equivalent dose[28] for opioid medication				
Mean (SD)	93.42 (98.79)	106.89 (103.24)	94.20 (103.72)	98.29 (101.81)
Median (min, max)	60.0 (30.0, 682.5)	60.0 (30.0, 450.0)	60.0 (30.0, 780.0)	60.0 (30.0, 780.0)
Disease characteristics, mean (SD)				
SBM frequency rate	1.05 (0.81)	1.01 (0.70)	1.14 (0.84)	1.07 (0.78)
CSBM frequency rate	0.22 (0.45)	0.26 (0.46)	0.27 (0.48)	0.25 (0.46)
No. of days with SBM per week	0.99 (0.76)	0.97 (0.68)	1.04 (0.75)	1.00 (0.73)
Stool consistency*	2.07 (1.18)	2.25 (1.19)	2.19 (1.03)	2.18 (1.13)
Straining†	3.71 (0.82)	3.50 (0.92)	3.40 (0.94)	3.53 (0.90)
Abdominal bloating‡	4.35 (2.06)	4.48 (1.91)	4.53 (2.10)	4.46 (2.02)
Abdominal pain‡	4.41 (2.16)	4.21 (2.05)	4.27 (2.34)	4.29 (2.18)
Abdominal discomfort‡	4.37 (1.96)	4.40 (1.92)	4.60 (2.12)	4.46 (2.00)
OIC severity§	3.65 (0.61)	3.62 (0.65)	3.62 (0.67)	3.63 (0.64)
Conditions relevant to study inclusion-related opioid use in ≥5% of patients in any treatment group, n (%)				
Back pain	60 (76.9)	68 (78.2)	65 (74.7)	193 (76.6)
Neck pain	9 (11.5)	13 (14.9)	8 (9.2)	30 (11.9)
Arthralgia	7 (9.0)	4 (4.6)	4 (4.6)	15 (6.0)
Osteoarthritis	1 (1.3)	6 (6.9)	4 (4.6)	11 (4.4)
Pain	3 (3.8)	1 (1.1)	5 (5.7)	9 (3.6)

Higher scores indicate greater symptom severity for straining, abdominal bloating, and OIC severity.
* Stool consistency assessed daily for each bowel movement using a 7-point ordinal Bristol Stool Form Scale (1 = separate hard lumps like nuts [difficult to pass]; 7 = watery, no solid pieces [entirely liquid]).
† Straining assessed daily for each BM using a 5-point (1-5) scale.
‡ Abdominal bloating, pain, and discomfort assessed daily using an 11-point (0-10) numerical rating scale.
§ OIC severity assessed weekly using a 5-point (1-5) ordinal rating scale.
BM, bowel movement; BMI, body mass index; CSBM, complete spontaneous bowel movement; OIC, opioid-induced constipation; SBM, spontaneous bowel movement.

response were 1.37 and 1.92 times higher among patients treated with linaclotide 145 μg (P = 0.3332) and 290 μg (P = 0.0506), respectively, vs placebo-treated patients.

3.3.2. Changes from baseline in 8-week stool consistency, straining, and abdominal bloating

Change from baseline in 8-week stool consistency significantly improved in favor of linaclotide-treated patients. Specifically, BSFS scores increased (indicating softer stools) by 1.7 and 1.9 points for linaclotide 145 and 290 μg, respectively, vs 0.9 for placebo (P < 0.001 for both comparisons of linaclotide vs placebo) (**Fig. 2B**). Mean (SD) 8-week stool consistency scores were 3.8 (1.4) and 4.0 (1.3) for linaclotide 145 and 290 μg, respectively, vs 3.0 (1.2) for placebo. The change from baseline in 8-week straining was −1.2 and −1.4 for linaclotide 145 and 290 μg, respectively, vs −0.8 for placebo. The mean reduction in straining was significant for both linaclotide doses (145 μg, P = 0.0017; 290 μg, P < 0.0001) vs placebo (**Fig. 2B**). The change from baseline in 8-week abdominal bloating

was −1.0 (P = 0.8720) and −1.6 (P = 0.0034) for linaclotide 145 and 290 μg, respectively, vs −1.0 for placebo (**Fig. 2B**).

3.3.3. Time to first spontaneous bowel movement

The median time to first SBM was 26.5 hours (95% CI 21.8-45.0) and 28.7 hours (95% CI 23.5-47.0) for linaclotide 145 and 290 μg groups, respectively, vs 47.1 hours (95% CI 25.0-71.8) for placebo. At any time, the likelihood of achieving the first SBM was 1.3 and 1.4 times higher among patients treated with linaclotide 145 μg (P = 0.1429) and 290 μg (P = 0.0287), respectively, vs placebo.

3.4. Additional efficacy endpoints

3.4.1. Durable responders: 6-/8- + last 3-/4-week SBM 3 + 1 responder rate

The durable response rates were similar to the 3 + 1 for 6-/8-week SBM responder rates. Overall, 36.8%, 42.5%, and 30.8% of patients in the linaclotide 145 μg, linaclotide 290 μg, and
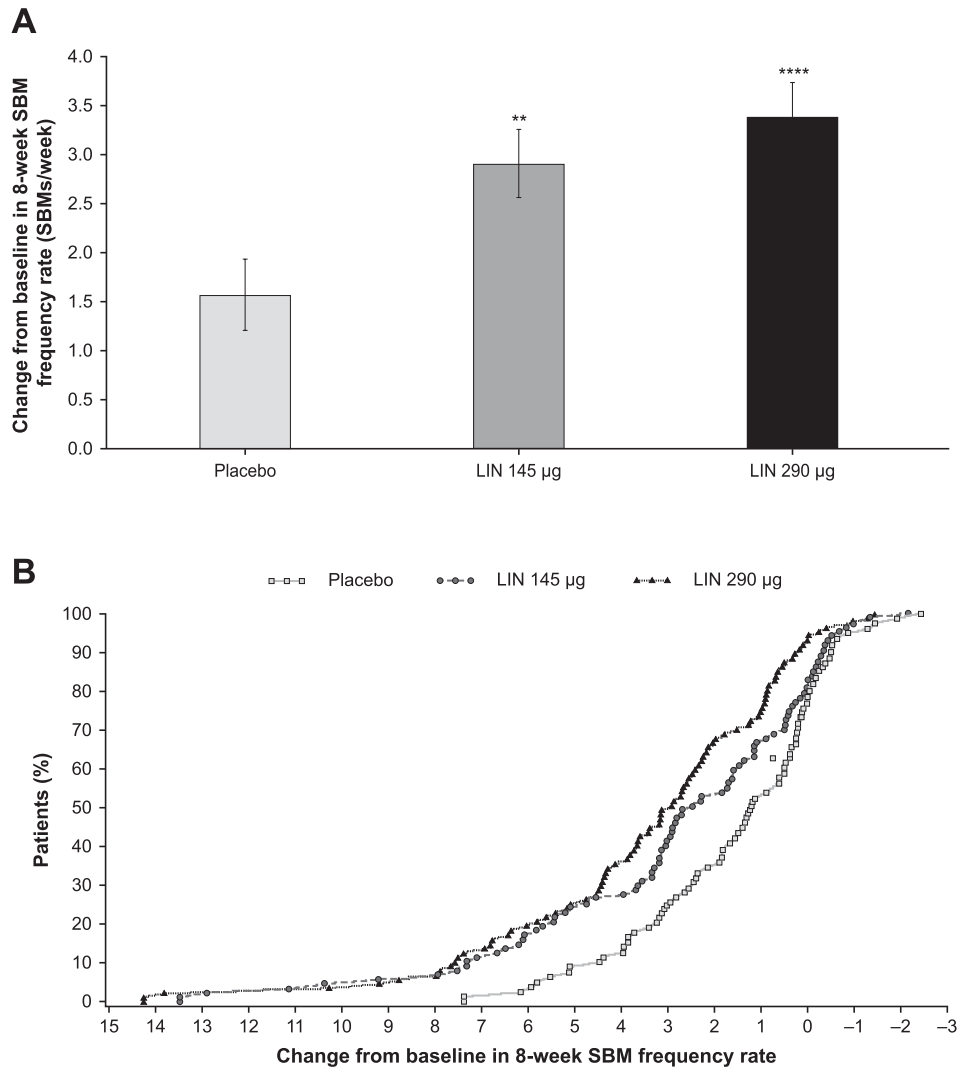
Figure 1. (A) Change from baseline in 8-week SBM frequency rate[a]; (B) distribution of change from baseline in the 8-week SBM frequency rate. All analyses were conducted in the ITT population. [a]Data are presented as least squares mean ± SD. P values were calculated from analysis of covariance model t-tests comparing specified treatment groups, controlling for geographic region and baseline value. **$P < 0.01$; ****$P < 0.0001$. ITT, intent-to-treat; LIN, linaclotide; SBM, spontaneous bowel movement.

placebo groups, respectively, achieved this more stringent endpoint (**Fig. 3A**). The odds of achieving a durable response were 1.3 and 1.9 times higher among patients treated with linaclotide 145 μg ($P = 0.3834$) and 290 μg ($P = 0.0734$), respectively, vs placebo.

3.4.2. Change from baseline in weekly spontaneous bowel movement frequency rate, weekly and 8-week opioid-induced constipation severity, and treatment satisfaction

The changes from baseline in SBM frequency rate (SBMs/week) at week 1 were 3.1 ($P = 0.0026$) and 3.6 ($P < 0.0001$) for linaclotide 145 and 290 μg, respectively, vs 1.5 for placebo (**Fig. 3B**). Furthermore, significantly greater improvements in SBM frequency rates were maintained in favor of both linaclotide groups for each week across the 8-week study period, except for the linaclotide 145 μg group at week 7 ($P > 0.05$).

The changes from baseline in weekly OIC severity scores also identified significant improvements vs placebo from week 1 to week 4 in the linaclotide 145 μg group and from week 1 to week 8 in the linaclotide 290 μg group (**Fig. 3C**). The changes from

baseline in 8-week OIC severity scores were −1.0 ($P = 0.0088$) and −1.1 ($P < 0.0001$) for linaclotide 145 μg and 290 μg, respectively, vs −0.6 for placebo.

The mean treatment satisfaction scores at week 1 were 2.8, 2.8, and 2.2 in the linaclotide 145 μg, linaclotide 290 μg, and placebo groups, respectively ($P = 0.0004$ for both linaclotide groups vs placebo) (**Fig. 3D**). These improvements were maintained throughout the 8-week treatment period in favor of both linaclotide groups, except for the linaclotide 145 μg group at week 7.

3.4.3. Adequate relief of opioid-induced constipation symptom responder rates

The 6-/8-week adequate relief of OIC symptom responder rates were 51.7%, 54.0%, and 33.3% in the linaclotide 145 μg, linaclotide 290 μg, and placebo groups, respectively (**Fig. 3E**). The odds of achieving this response were 2.1 times ($P = 0.0210$) and 2.4 times ($P = 0.0066$) higher among patients treated with linaclotide 145 and 290 μg, respectively, vs placebo.
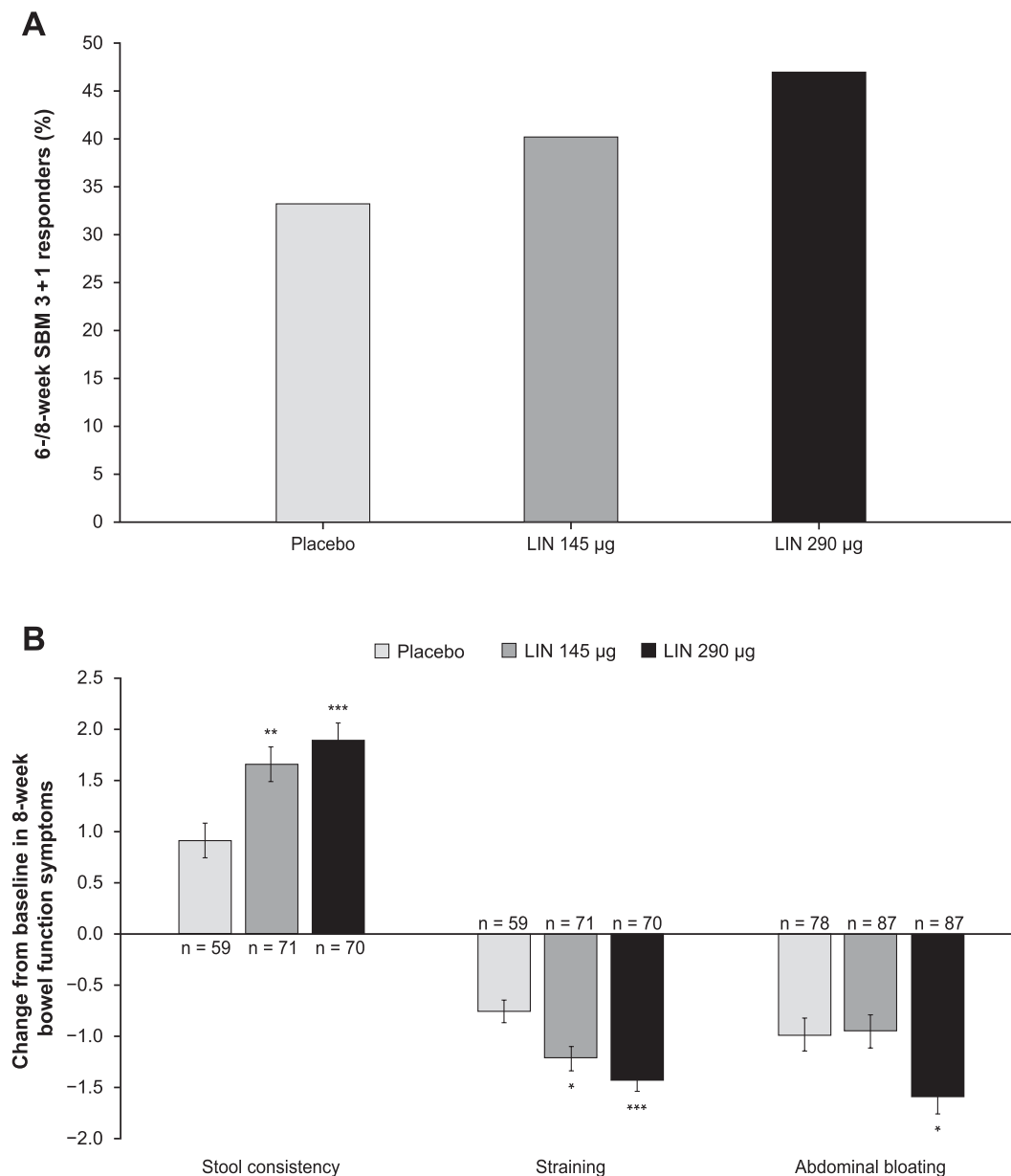
Figure 2. (A) 6-/8-week SBM 3 + 1 responders[a]; (B) change from baseline in 8-week bowel function symptoms. Daily assessment of stool consistency for each bowel movement was performed using the 7-point Bristol Stool Form Scale (1 = separate hard lumps like nuts [difficult to pass]; 7 = watery, no solid pieces [entirely liquid]); straining for each bowel movement was assessed using a 5-point (1-5) scale, abdominal bloating using an 11-point (0-10) numerical rating scale, and weekly assessment of opioid-induced constipation severity using a 5-point (1-5) ordinal rating scale, with higher scores indicating greater symptom severity for straining, abdominal bloating, and opioid-induced constipation. All analyses were conducted in the ITT population. [a]Data are presented as the proportion of patients in each group who met the weekly SBM 3 + 1 responder criteria for ≥6 of the 8 weeks of the treatment period. P values were calculated from analysis of covariance model t-tests comparing specified treatment groups, controlling for geographic region and baseline value. *P ≤ 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. ITT, intent-to-treat; LIN, linaclotide; SBM, spontaneous bowel movement.

3.4.4. Change from baseline in percent of patient-reported days using rescue medication

For the linaclotide 145 μg, linaclotide 290 μg, and placebo groups, the percentages of days that patients reported using rescue medication at baseline were 21.5%, 17.9%, and 20.9%, respectively; during the treatment period, these percentages were reduced to 14.2%, 7.5%, and 16.6%. The reduction for linaclotide was greatest in the 290 μg group (P = 0.0156).

3.5. Safety

Six patients receiving linaclotide 290 μg discontinued treatment due to AEs compared with 2 patients receiving linaclotide 145 μg

and 3 receiving placebo. Diarrhea was the most common TEAE, reported by 24 (27.6%), 32 (36.8%), and 13 (16.7%) patients in the linaclotide 145 μg, linaclotide 290 μg, and placebo groups, respectively (**Table 2**). The majority (51.8%) of linaclotide-treated patients who reported diarrhea did so within the first week of treatment; 10 patients (5.7%) experienced an episode of diarrhea on day 1. For most patients in the safety population, treatment-related diarrhea was mild to moderate in severity; there were no serious AEs related to diarrhea. Diarrhea led to discontinuation in 1 (1.1%), 5 (5.7%), and 1 (1.3%) patient in the linaclotide 145 μg, linaclotide 290 μg, and placebo groups, respectively. Other TEAEs leading to discontinuation were back pain and edema in 1 patient each (1.1%) in the linaclotide 145 and 290 μg groups, respectively, with none in the placebo group. All other TEAEs
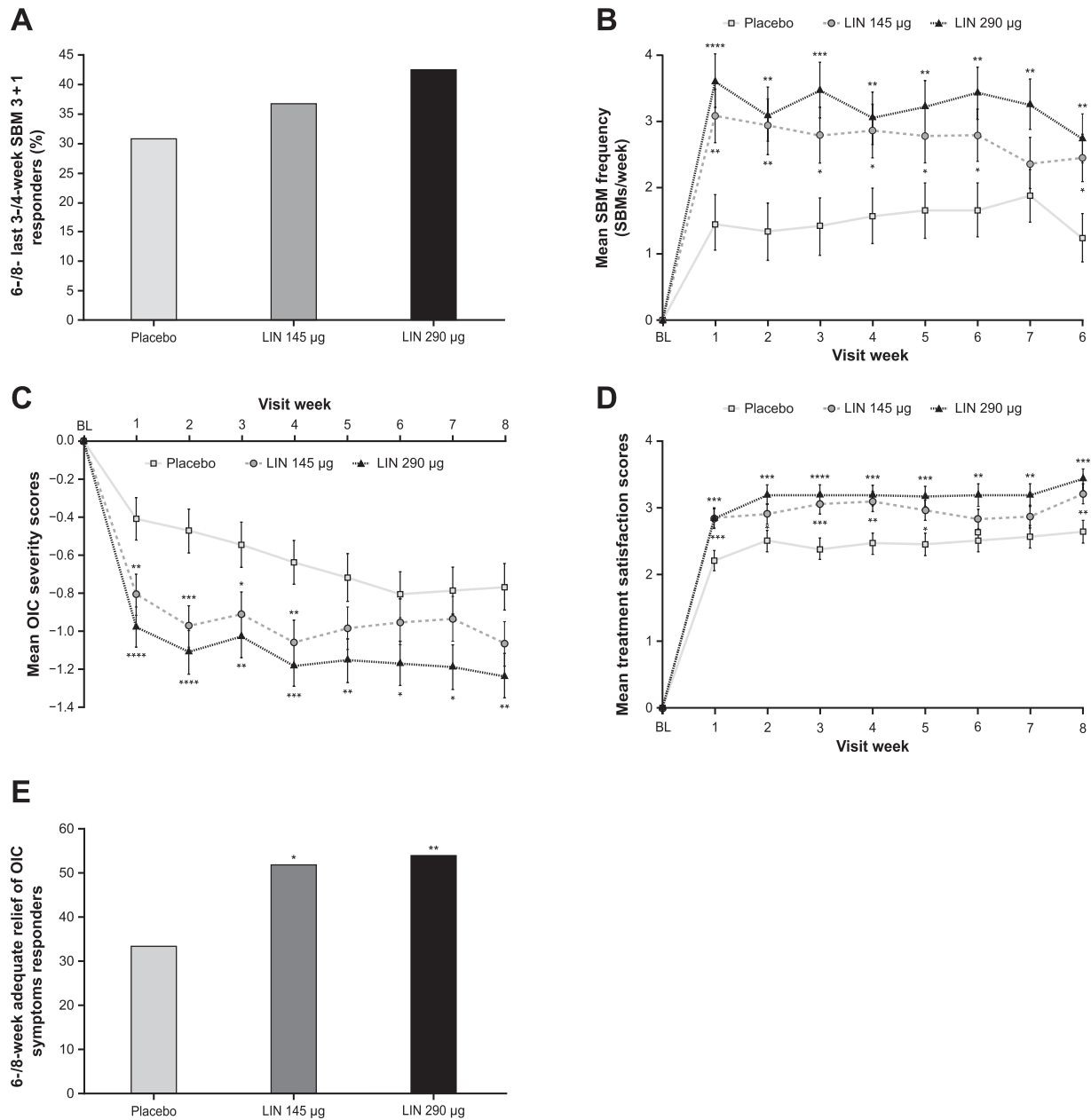
Figure 3. (A) 6-/8- + last 3-/4-week SBM 3 + 1 responders[a]; change from baseline in weekly (B) SBM frequency, (C) OIC severity scores, (D) treatment satisfaction, and (E) 6-/8-week adequate relief of OIC symptom response[b]. All analyses were conducted in the ITT population. Data are presented as least squares mean ± SD. P values were calculated using mixed-effect model for repeated measures t-tests comparing specified treatment groups, controlling for week, geographic region, and baseline value, with treatment group-by-week and baseline value-by-week as interaction terms; P values for adequate relief responder rates were calculated using Cochran–Mantel–Haenszel tests comparing specified treatment groups, controlling for geographic region. *$P \leq 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$. Weekly assessments of OIC severity and treatment satisfaction were performed using a 5-point (1-5) ordinal rating scale, with higher scores indicating greater OIC severity and greater satisfaction. [a]Data are presented as the proportion of patients in each group who met the weekly SBM 3 + 1 responder criteria for ≥6 of the 8 weeks and ≥3 of the last 4 weeks of the treatment period. [b]Data are presented as the proportion of patients in each group who reported adequate relief of OIC symptoms for ≥6 weeks of the 8-week treatment period. BL, baseline; ITT, intent-to-treat; LIN, linaclotide; OIC, opioid-induced constipation; SBM, spontaneous bowel movement.

occurred less frequently and at similar rates between the treatment groups. The majority (>95%) of reported TEAEs for all patients were mild or moderate in severity.

Serious AEs were reported by 1 patient (1.1%) in the linaclotide 290 μg group compared with 5 patients (6.4%) in the placebo group. No serious AEs were reported in the linaclotide 145 μg group. The 1 serious AE (transient ischemic attack) experienced by a linaclotide-treated patient was not considered to be treatment-related. One death occurred during the study in

a placebo-treated patient (cardiac arrest in a patient with a medical history of coronary artery disease, myocardial infarction, and type 2 diabetes mellitus) and was considered unrelated to treatment.

There were no clinically meaningful differences between the placebo and linaclotide treatment groups in the incidence of abnormal electrocardiogram findings, physical examination findings, laboratory parameters, or vital signs. There were no differences between the placebo and linaclotide treatment

Incidence of overall and treatment-related TEAEs in the safety population.

n (%)	Placebo (n = 78)	Linaclotide 145 μg/d (n = 87)	Linaclotide 290 μg/d (n = 87)	Linaclotide total (N = 174)
Any TEAE	30 (38.5)	40 (46.0)	48 (55.2)	88 (50.6)
≥1 treatment-related TEAE	9 (11.5)	22 (25.3)	29 (33.3)	51 (29.3)
Any TEAEs in ≥2% of patients				
Diarrhea	13 (16.7)	24 (27.6)	32 (36.8)	56 (32.2)
Back pain	1 (1.3)	3 (3.4)	2 (2.3)	5 (2.9)
Soft feces	0	2 (2.3)	3 (3.4)	5 (2.9)
Abdominal pain	3 (3.8)	4 (4.6)	0	4 (2.3)
Sinusitis	0	2 (2.3)	1 (1.1)	3 (1.7)
Upper respiratory tract infection	0	3 (3.4)	0	3 (1.7)
Flatulence	0	2 (2.3)	0	2 (1.1)
Musculoskeletal pain	0	0	2 (2.3)	2 (1.1)
Pain in extremity	0	2 (2.3)	0	2 (1.1)
Pyrexia	1 (1.3)	2 (2.3)	0	2 (1.1)
Viral gastroenteritis	2 (2.6)	0	1 (1.1)	1 (0.6)
Nausea	4 (5.1)	0	1 (1.1)	1 (0.6)
Arthralgia	2 (2.6)	0	0	0
Fall	2 (2.6)	0	0	0
Oropharyngeal pain	2 (2.6)	0	0	0
Treatment-related TEAEs in ≥2% of patients				
Diarrhea	6 (7.7)	20 (23.0)	27 (31.0)	47 (27.0)
Soft feces	0	2 (2.3)	2 (2.3)	4 (2.3)
Abdominal pain	1 (1.3)	3 (3.4)	0	3 (1.7)
Flatulence	0	2 (2.3)	0	2 (1.1)

TEAE, treatment-emergent adverse event.

groups for pain requiring an opioid (assessed using the Brief Pain Inventory–Short Form), suggesting that linaclotide has no effect on the efficacy of opioid treatments.

4. Discussion

Opioid-induced constipation is the most common GI adverse effect attributed to opioid use (number needed to harm: ~3.3) and can lead to reductions in, or discontinuation of, opioid therapy that may result in inadequate pain control and decreased quality of life.[3–6] Lifestyle modifications and over-the-counter laxatives are recommended first-line therapies for OIC[15]; however, they do not directly target the underlying etiology of OIC and are ineffective in approximately 50% to 90% of patients with self-identified OIC.[14,25,44] When these measures are ineffective, recent guidelines from the American Gastroenterological Association Institute recommend the initiation of prescription laxatives.[15] Linaclotide functions locally in the intestinal lumen, activating guanylate cyclase-C, stimulating fluid secretion, and increasing GI transit, which potentially mitigates the constipating effects of opioids on the GI tract.

The doses of linaclotide evaluated in this study are approved for the treatment of constipation in patients with IBS-C (290 μg/day) and CIC (145 μg/day).[41] Both doses significantly increased SBM frequency rates (SBMs/week) compared with placebo in patients with OIC related to noncancer pain syndromes, with a larger response favoring patients treated with linaclotide 290 μg. In addition, the higher linaclotide dose demonstrated greater improvements for other important parameters of OIC, including straining, abdominal bloating, and time to first SBM, compared with placebo, and both doses resulted in significantly greater increases in SBM frequency rates at week 1, providing patients with rapid symptom relief.

Although not directly assessed in head-to-head trials, comparisons of OIC treatments for noncancer pain patients reveal that linaclotide provides responder rates (47.1% for 6-/8-week SBM 3 + 1 and 42.5% for 6-/8- + last 3-/4-week SBM 3 + 1) comparable with those of the FDA-approved peripherally acting μ-opioid receptor antagonists, based on their similar primary efficacy endpoints of 9-/12- + last 3-/4-week SBM 3 + 1 responder rates (44.4% for naloxegol and 52.5% for naldemedine).[13,22] In addition, when compared to clinical trial results achieved with another secretagogue (lubiprostone), linaclotide 145 and 290 μg provided comparable changes from baseline in 8-week SBM frequency rates of 2.9 and 3.5, respectively.[16,23] Changes from baseline in 8-week SBM frequency rates in the placebo groups were also comparable across the current study and the lubiprostone trials.

Improvements in other efficacy endpoints, such as time to first SBM and reduction in OIC symptoms, were also similar between linaclotide and lubiprostone. Treatment with linaclotide 145 and 290 μg reduced median time to first SBM to 26.5 and 28.7 hours, respectively, vs a reduction in median time to first SBM to 23.5 or 28.5 hours with lubiprostone.[16,23] Furthermore, improvements from baseline in 8-week constipation symptom severity were greater with linaclotide in this study vs those reported for lubiprostone (1.9, 1.4, 1.6, and 1.1 vs ~1.0, ~1.1, ~0.6, and ~0.7 for stool consistency, straining, abdominal bloating, and OIC severity, respectively).[23] Although these comparisons are not based on head-to-head trials between the 2 medications, the current data support the efficacy of linaclotide in this patient population.

Safety data revealed that both doses of linaclotide are well tolerated in patients with OIC, and the results are consistent with the established safety profile of linaclotide in patients with IBS-C or CIC. The most commonly reported AE in linaclotide-treated patients was diarrhea, with the majority of cases characterized as

mild in severity. Rates of severe diarrhea (1.1%) and treatment discontinuation due to diarrhea (3.4%) were low and also consistent with previous linaclotide studies in IBS-C (2% severe diarrhea and 5% discontinuations due to diarrhea) and CIC (2% severe diarrhea and 2% to 5% discontinuations due to diarrhea).[27,28,32,41,42] Furthermore, the placebo-adjusted rate of discontinuation due to diarrhea in this study (4.4% for linaclotide 290 μg) is similar to the placebo-adjusted rate of discontinuation due to diarrhea from prior randomized trials (3.7%), as shown in a pooled safety analysis.[30]

The overall incidence of diarrhea in placebo-treated (16.7%) and linaclotide-treated (32.2%) patients with OIC in this study was higher than rates observed for other OIC medications (which are generally <10%). The rates were also higher than those observed in previous linaclotide placebo-controlled studies in patients with IBS-C and CIC (14% to 20% vs 3% to 5% in the linaclotide and placebo groups, respectively), but the absolute differences in diarrhea rates are comparable.[1,19,27,33,41,42]

Although the causative mechanism for constipation in patients with OIC differs from that in patients with IBS-C and CIC, the exact reasons for the higher incidence of diarrhea are not clear in the current study. Differences in study design are known to alter AE reporting rates, and because linaclotide is available for other indications, it is plausible that an existing knowledge of expected diarrhea contributed to the higher diarrhea incidence reported in this study.

Treatment with linaclotide 290 μg/day improved overall treatment satisfaction scores beginning at week 1, and these changes were sustained throughout the entire 8-week study period. These findings are consistent with previous results showing similar improvements in treatment satisfaction for both IBS-C and CIC.[38]

The study was accurately powered to evaluate the primary endpoint; however, the sample size of the treatment groups was small (<100) and study duration was short (8 weeks). Other than declaration of the primary endpoint, there were no adjustments for multiple comparisons, and P values are presented for descriptive purposes only. Furthermore, although linaclotide demonstrated efficacy and safety over the 8-week treatment period, no follow-up or extension period was included to confirm the results over time or to assess for rebound once therapy was discontinued. Extrapolating from data from previous IBS-C and CIC trials, we surmise that the likelihood of rebound constipation would be low. Finally, although enrolled patients agreed to maintain a stable opioid dosing regimen throughout the study, opioid dosing compliance and the impact of any opioid dosing variations on the study results were not evaluated.

In conclusion, patients with OIC related to chronic noncancer pain syndromes benefited from treatment with both the 145 and 290 μg/day doses of linaclotide. Patients demonstrated significant increases in SBM frequency beginning in the first week of treatment, with greater improvements in constipation-associated symptoms and reductions in OIC severity compared with placebo. Both linaclotide doses were well tolerated and exhibited a safety profile consistent with previous studies in IBS-C and CIC. Thus, linaclotide offers the potential for a unique treatment option in patients with OIC related to opioid therapy administered for chronic noncancer pain.

Conflict of interest statement

D.M. Brenner serves as a consultant, advisor, and speaker for Allergan and Ironwood Pharmaceuticals, Inc. B.D. Cash serves as a consultant, advisor, and speaker for Allergan and Salix Pharmaceuticals and as a consultant for Ironwood Pharmaceuticals, Inc. C.E. Argoff serves as a consultant for Shionoghi, Inc and as a speaker for DSI. S.M. Fox, W. Bochenek, and P. D'Astoli are employees of, and hold stock and stock options in, Allergan plc. R.E. Blakesley is a former employee of, and holds stock in, Allergan plc. C.R. O'Dea is an employee of, and holds stock and stock options in, Ironwood Pharmaceuticals, Inc. D.S. Reasner is a former employee of, and holds stock in, Ironwood Pharmaceuticals, Inc.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A914.

References

[1] Andresen V, Miehlke S, Beck E, Wiseman G, Layer P. Efficacy and tolerability of linaclotide in the treatment of irritable bowel syndrome with constipation in a realworld setting—results from a German noninterventional study. Z Gastroenterol 2018;56:738–44.
[2] Argoff CE, Brennan MJ, Camilleri M, Davies A, Fudin J, Galluzzi KE, Gudin J, Lembo A, Stanos SP, Webster LR. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. Pain Med 2015;16:2324–37.
[3] Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. J Opioid Manag 2009;5:137–44.
[4] Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med 2009;10:35–42.
[5] Brenner DM, Chey WD. An evidence-based review of novel and emerging therapies for constipation in patients taking opioid analgesics. Am J Gastro Suppl 2014;2:38–46.
[6] Brenner DM, Stern E, Cash BD. Opioid-related constipation in patients with non-cancer pain syndromes: a review of evidence-based therapies and justification for a change in nomenclature. Curr Gastroenterol Rep 2017;19:12.
[7] Busby RW, Bryant AP, Bartolini WP, Cordero EA, Hannig G, Kessler MM, Mahajan-Miklos S, Pierce CM, Solinga RM, Sun LJ, Tobin JV, Kurtz CB, Currie MG. Linaclotide, through activation of guanylate cyclase C, acts

locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. Eur J Pharmacol 2010;649:328–35.

[8] Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. Am J Gastroenterol 2011;106:835–42.

[9] Camilleri M, Bharucha AE, Ueno R, Burton D, Thomforde GM, Baxter K, McKinzie S, Zinsmeister AR. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G942–47.

[10] Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil 2014;26:1386–95.

[11] Castro J, Harrington AM, Hughes PA, Martin CM, Ge P, Shea CM, Jin H, Jacobson S, Hannig G, Mann E, Cohen MB, Macdougall JE, Lavins BJ, Kurtz CB, Silos-Santiago I, Johnston JM, Currie MG, Blackshaw LA, Brierley SM. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-c and extracellular cyclic guanosine 3′, 5′-monophosphate. Gastroenterology 2013;145: 1334–46.e11.

[12] Centers for Disease Control and Prevention. 2018 Annual surveillance report of drug-related risks and outcomes. 2018. Available at: https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf. Accessed February 28, 2019.

[13] Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 2014;370:2387–96.

[14] Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. Clinicoecon Outcomes Res 2014;6:269–81.

[15] Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the medical management of opioid-induced constipation. Gastroenterology 2019;156:218–26.

[16] Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med 2014;15:1825–34.

[17] Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006;130:1377–90.

[18] Drossman DA, Chey W, Panas R, Wahle A, Scott C, Ueno R. Lubiprostone significantly improves symptom relief rates in adults with irritable bowel syndrome and constipation (IBS-C): data from two twelve-week, randomized, placebo-controlled, double-blind trials. Gastroenterology 2007;132:2586–87.

[19] Emmanuel A, Mclaughlin J, Mclain-Smith S, Rance M, Agrawal A, Allen PB, Arebi N, Brown S, Eugenicos M, Farmer AD, Yiannakou Y. UK clinical experience at 12 weeks with linaclotide for irritable bowel syndrome with constipation. United Eur Gastroenterol J 2016;4(5 suppl):A295–96.

[20] Eutamene H, Bradesi S, Larauche M, Theodorou V, Beaufrand C, Ohning G, Fioramonti J, Cohen M, Bryant AP, Kurtz C, Currie MG, Mayer EA, Bueno L. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. Neurogastroenterol Motil 2010;22:312-e84.

[21] Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. Am J Gastroenterol 2013; 108:1566–74.

[22] Hale M, Wild J, Reddy J, Yamada T, Arjona Ferreira JC. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials. Lancet Gastroenterol Hepatol 2017;2:555–64.

[23] Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol 2015;110:725–32.

[24] Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. PAIN 2004;112:372–80.

[25] Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. Gastroenterol Res Pract 2014;2014:141737.

[26] Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel disorders. Gastroenterology 2016;150:1393–407.e5.

[27] Lacy BE, Schey R, Shiff SJ, Lavins BJ, Fox SM, Jia XD, Blakesley RE, Hao X, Cronin JA, Currie MG, Kurtz CB, Johnston JM, Lembo AJ. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. PLoS One 2015;10: e0134349.

[28] Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, Shao JZ, Lavins BJ, Currie MG, Fitch DA, Jeglinski BI, Eng P, Fox SM, Johnston JM. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011;365:527–36.

[29] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–24.

[30] Nee JW, Johnston JM, Shea EP, Walls CE, Tripp K, Shiff S, Fox SM, Bochenek W, Weissman D, Currie MG, Lembo AJ. Safety and tolerability of linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation: pooled Phase 3 analysis. Expert Rev Gastroenterol Hepatol 2019;13:397–406.

[31] Nelson AD, Camilleri M. Opioid-induced constipation: advances and clinical guidance. Ther Adv Chronic Dis 2016;7:121–34.

[32] Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, Shi K, MacDougall JE, Shao JZ, Eng P, Fox SM, Schneier HA, Kurtz CB, Johnston JM. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107:1714–24.

[33] Rao SSC, Quigley EMM, Shiff SJ, Lavins BJ, Kurtz CB, MacDougall JE, Currie MG, Johnston JM. Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. Clin Gastroenterol Hepatol 2014;12:616–23.

[34] Silos-Santiago I, Hannig G, Eutamene H, Ustinova EE, Bernier SG, Ge P, Graul C, Jacobson S, Jin H, Liong E, Kessler MM, Reza T, Rivers S, Shea C, Tchernychev B, Bryant AP, Kurtz CB, Bueno L, Pezzone MA, Currie MG. Gastrointestinal pain: unraveling a novel endogenous pathway through uroguanylin/guanylate cyclase-C/cGMP activation. PAIN 2013;154:1820–30.

[35] Stein C. Opioids, sensory systems and chronic pain. Eur J Pharmacol 2013;716:179–87.

[36] Szigethy E, Knisely M, Drossman D. Opioid misuse in gastroenterology and non-opioid management of abdominal pain. Nat Rev Gastroenterol Hepatol 2018;15:168–80.

[37] Takeda Pharmaceuticals Inc. Amitza (lubiprostone) prescribing information. 2018. Available at: https://general.takedapharm.com/amitizapi. Accessed February 28, 2019.

[38] Taylor DCA, Abel JL, Doshi JA, Martin C, Buzinec P, Goolsby Hunter A, Essoi B, Reasner DS, Carson RT, Chey WD. Impact of linaclotide and stool form on bowel movement satisfaction in patients with irritable bowel syndrome with constipation or chronic idiopathic constipation: results from the CONTOR study:P342. American College of Gastroenterology Annual Scientific Meeting, Las Vegas, NV, 2016.

[39] Thomas J. Opioid-induced bowel dysfunction. J Pain Symptom Manage 2008;35:103–13.

[40] Thomas RH, Luthin DR. Current and emerging treatments for irritable bowel syndrome with constipation and chronic idiopathic constipation: focus on prosecretory agents. Pharmacotherapy 2015;35:613–30.

[41] US Food and Drug Administration. Linzess highlights of prescribing information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202811s013lbl.pdf#page=20. Accessed February 28, 2019.

[42] Videlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. Clin Gastroenterol Hepatol 2013;11:1084–92.

[43] Viscusi ER. Clinical overview and considerations for the management of opioid-induced constipation in patients with chronic noncancer pain. Clin J Pain 2018;35:174–88.

[44] Yoon SC, Bruner HC. Naloxegol in opioid-induced constipation: a new paradigm in the treatment of a common problem. Patient Prefer Adherence 2017;11:1265–71.