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

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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+ 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. Dianthea, 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.10,21,28 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 nonprescription 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 Pharma-
cuticals, UK/Daiichi-Sankyo, Japan), and naldemedine (Shionogi
Inc, Japan and Purdue Pharma LP, Stamford, CT).45 Lubiprostone
(Takeda Pharmaceuticals, Inc, Tokyo, Japan), a type-2 chloride
channel 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 Pharma-
cuticals, 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 mono-
phosphate, resulting in chloride and bicarbonate secretion into
the intestinal lumen, leading to elevated intestinal fluid and transit.
Moreover, increased extracellular cyclic guanosine monophos-
phate 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, laboratorv 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 pretreat-
ment period were eligible for the 8-week treatment period (Supple-
mental 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
instit utional review board or independent ethics committee
for each study center. The study was conducted in accor-
dance with the ethical principles of the Declaration of Helsinki
and compliant 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 move-
ments (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, mega-
colon, megarectum, descending perineum syndrome, solitary
rectal ulcer syndrome, fecal impaction that required hospitali-
zation, 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]);20,29,36,37 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 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 change from baseline in 8-week stool consistency, weekly OIC severity, 6-/8-week adequate relief responder rate, treatment satisfaction, changes from baseline in SBM frequency rate, and overall linaclotide treatment group (combined linaclotide 145 mg and 290 mg). 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, 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. 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 responders
The 6-/8-week SBM ≥ 3 responders 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
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-week SBM 3+ 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...
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 mg (P = 0.3834) and 290 mg (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.
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 2.](image-url)
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
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 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-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- and 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 −0.7, −0.6, and −0.7 for stool consistency, straining, abdominal bloating, and OIC severity, respectively). 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).  

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.  

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.  

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.  

The study was accurately powered to evaluate the primary endpoint; however, the sample size of the treatment groups was small (<110) 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 Shionogi, 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.  

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

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