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A Randomized, Placebo-Controlled Trial of Lubiprostone for Opioid-Induced Constipation in Chronic Noncancer Pain

M. Mazen Jamal, MD, MPH[1,2], Atoya B. Adams, MD, MBA[3], Jan-Peter Jansen, Dr med[4] and Lynn R. Webster, MD[5]

OBJECTIVES: **This multicenter, phase 3 trial evaluated oral lubiprostone for constipation associated with non-methadone opioids in patients with chronic noncancer-related pain.**

METHODS: **Adults with opioid-induced constipation (OIC; <3 spontaneous bowel movements [SBMs] per week) were randomized 1:1 to double-blind lubiprostone 24 μg or placebo twice daily for 12 weeks. The primary end point was the overall SBM response rate. Responders had at least moderate response (≥1 SBM improvement over baseline frequency) in all treatment weeks with available observed data, as well as full response (≥3 SBMs per week) for at least 9 of the 12 treatment weeks.**

RESULTS: **In total, 431 patients were randomized; 212 each received lubiprostone and placebo, and 7 were not treated. Overall, the SBM response rate was significantly higher for patients treated with lubiprostone vs. placebo (27.1 vs. 18.9%, respectively; *P*=0.030). Overall mean change from baseline in SBM frequency was significantly greater with lubiprostone vs. placebo (3.2 vs. 2.4, respectively; *P*=0.001). The median time to first SBM was significantly shorter with lubiprostone vs. placebo (23.5 vs. 37.7 h, respectively; *P*=0.004). Compared with placebo, the patients treated with lubiprostone exhibited significant improvements in straining (*P*=0.004), stool consistency (*P*<0.001), and constipation severity (*P*=0.010). No significant differences were observed in quality-of-life measures or the use of rescue medication; however, the percentage of patients who used rescue medication was consistently lower in the lubiprostone group than in the placebo group at months 1 (34.9 vs. 37.7%), 2 (23.4 vs. 26.6%), and 3 (20.5 vs. 22.0%). Adverse events (AEs) >5% were diarrhea, nausea, vomiting, and abdominal pain (lubiprostone: 11.3, 9.9, 4.2, and 7.1%, respectively; placebo, 3.8, 4.7, 5.2, and 0%, respectively). None of the serious AEs (lubiprostone, 3.3%; placebo, 2.8%) were related to lubiprostone.**

CONCLUSIONS: **Lubiprostone significantly improved symptoms of OIC and was well tolerated in patients with chronic noncancer pain.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Opioids are recommended for managing moderate-to-severe chronic noncancer pain (1,2); however, opioid-induced constipation (OIC) is often a treatment-limiting adverse effect among these patients. The incidence of constipation in clinical trials of opioids for chronic pain has been estimated at 15% (3), whereas prevalence in a community-based survey exceeded 80% (4). Although the patients may develop tolerance to other opioid-related adverse effects, constipation persists and negatively affects patient health-related quality of life (HRQOL) (4). OIC may lead to the discontinuation of opioids, leading to poor pain control. Furthermore, patients who decrease their opioid dose to relieve constipation may subsequently increase their dose in response to worsening pain caused by the underlying

[1]Department of Internal Medicine, Long Beach VA Medical Center, Long Beach, California, USA; [2]Department of Medicine, UCI College of Medicine, Irvine, California, USA; [3]AB Clinical Trials, Las Vegas, Nevada, USA; [4]SZ Schmerzzentrum Berlin GmbH, Berlin, Germany; [5]PRA Health Sciences, Salt Lake City, Utah, USA. **Correspondence:** M. Mazen Jamal, MD, MPH, Long Beach VA Medical Center, 5901 East 7th Street # 153-PCSC, Long Beach, California 90822, USA. E-mail: mazen.jamal@va.gov

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pain condition or the constipation itself, thus exacerbating constipation.

Although the definitions vary, OIC is characterized by infrequent and incomplete bowel movements (BMs), straining, and hard, dry stool consistency; additional gastrointestinal symptoms include abdominal discomfort, pain, and bloating (5). OIC encompasses both peripheral and central elements; peripherally, the opioid receptor activation delays gastric transit, reduces secretions, and promotes the reuptake of water and electrolytes, whereas centrally the opioids may decrease autonomic response in the gut (6). Long-term use of symptomatic treatments (e.g., laxatives) is not well supported by clinical trial data, and their effectiveness is limited (7).

Lubiprostone is an orally active prostone that locally and selectively activates ClC-2 chloride channels to enhance the intestinal fluid secretion without altering the serum electrolyte levels (8–10). Orally administered lubiprostone capsules are approved by the US Food and Drug Administration for chronic idiopathic constipation (CIC) in adults (24 μg twice daily (BID)) and irritable bowel syndrome with constipation in adult women (8 μg BID) (10). In 2013, oral lubiprostone was also approved for OIC in adults with chronic noncancer pain (24 μg BID) (10). Lubiprostone has a well-documented safety record in clinical studies (N>3,500) and 8 years of postmarketing experience.

The primary objective of this placebo-controlled study was to determine the efficacy and safety of lubiprostone 24 μg BID administered over the course of 12 weeks for the treatment of OIC in patients on opioid therapy for chronic noncancer-related pain.

METHODS

Study design

This randomized, double-blind, placebo-controlled, parallel-group phase 3 safety and efficacy study (NCT01298219) was conducted at 103 US and EU general practice, internal medicine, and specialty sites between December 2010 and November 2011.

All sites received an institutional review board approval; all patients provided approved informed consent. The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and Guidance on Good Clinical Practice (11).

Study population

Included patients were men and nonpregnant women, aged ≥18 years, treated for chronic noncancer pain with a stable opioid dose for ≥30 days, and diagnosed with OIC. Patients were excluded if the constipation was due to some other secondary cause and not due to the use of opioids. Patients with a history of chronic constipation (≥90 days) were included only if their constipation was exacerbated by the initiation of opioid treatment. OIC was defined as an average of <3 spontaneous BMs (SBMs) per week without the use of a laxative or stool softener during the last 2 weeks of the 3-week screening period and ≥1 of the following symptoms for ≥25% of SBMs during the same period: hard or very hard stools, sensation of incomplete evacuation, or moderate to very severe straining. An opioid dose was considered stabilized if there was no actual or anticipated change exceeding ±30% in morphine-equivalent daily dose (MEDD). Patients using antidepressants or fiber supplements had to have been receiving a stable dose for ≥30 days before screening.

Patients were excluded if they had anatomic or organ disorders of the large or small bowel or suspected secondary causes of constipation for which the origin was dietary (e.g., malnutrition), neurologic (e.g., spinal cord disorder), congenital, or endocrine (e.g., hypothyroidism or diabetes) in nature. Patients who were being treated with methadone or its congeners (e.g., propoxyphene, levomethadyl acetate, and acetylmethadol hydrochloride) were not eligible to participate in the study.

Study treatment

After a 3-week screening period, patients were randomized 1:1 to identical-appearing capsules of lubiprostone 24 μg or placebo BID, administered with meals and 8 oz of fluid, for 12 weeks. INC Research (formerly Kendle) developed, validated, and created the randomization code and kit randomization for the study. Study medication was assigned to patients according to the randomization schedule via an interactive voice response system. The patients, investigators, and all other clinical research and laboratory personnel were blinded to the randomized assignments throughout the study period. Compliance was documented by study personnel based on the medications dispensed and returned; patients tracked the medication use via electronic diaries.

At the investigator's discretion, the dose could be reduced to once daily (QD) permanently or temporarily if severe nausea, severe diarrhea, or another adverse event (AE; e.g., other gastrointestinal symptoms) persisted for ≥3 days. Rescue medication was permitted if no BM occurred within a 3-day period, but not within 24 h before and 72 h after the first dose of study medication. Initial rescue medication was a bisacodyl 10-mg suppository. If that failed, patients were permitted a repeat dose or a saline enema. If both regimens failed, short-term rescue medication (except polyethylene glycol 3350, methylnaltrexone, and prucalopride) could be prescribed at the investigator's discretion. With the exception of rescue medication, as noted previously, the use of anticholinergics, antispasmodics, or cholinesterase inhibitors; antidiarrheal, anticonstipation, prokinetic, or laxative agents; tricyclic antidepressants; other medications that relieve or cause constipation, bloating, or constipation-related symptoms; and opioid antagonists (e.g., naloxone, naltrexone, nalmefene, methylnaltrexone, and alvimopan) was not allowed during the study.

Efficacy assessments

Clinical examinations occurred on weeks 4, 8, and 12; interim telephone assessments were conducted at weeks 1, 6, and 10. The primary efficacy end point was the overall SBM response rate, based on constipation events recorded daily in electronic patient diaries. Overall responders were defined as reporting at least moderate response (≥1 SBM improvement over baseline frequency) for all treatment weeks for which observed data were available, as well as

a full response (additional ≥3 SBMs per week) for at least 9 of the 12 treatment weeks. Secondary end points included change from baseline in SBM frequency at weeks 8, 12, and overall; percentage of patients with a first SBM within 24 and 48 h postdose; weekly responder rates; and HRQOL (PAC-QOL, Patient Assessment of Constipation-Quality of Life) (12) and EQ-5D (EuroQoL-5 Dimensions) (13). Additional secondary end points included overall mean change from baseline for straining associated with SBMs, stool consistency, constipation severity, abdominal bloating, and abdominal discomfort.

Safety assessments

Treatment-emergent AEs (TEAEs) were recorded from the first dose of study medication until 7 days after the last dose; investigators classified AE severity. At each scheduled clinic visit, physical examinations were conducted, and clinical laboratory assays (hematology panel, chemistry panel, and urinalysis) and vital signs were recorded. Additional safety measurements included assessments of nausea (FLIE, Functional Living Index-Emesis), interference of opioid analgesic effect (BPI-SF, Brief Pain Inventory short form), opioid dose, and rescue medication usage. A follow-up visit conducted 2 weeks after treatment discontinuation documented any subsequent AEs or concomitant medications.

Statistical analysis

The study sponsor analyzed the data. Assuming a 20% discontinuation rate by week 9, it was estimated that an initial sample size of 420 patients would yield 336 evaluable patients (168 patients in each treatment group). This final sample size would provide at least 95% statistical power to detect an improvement in overall responders for lubiprostone compared with placebo, based on response rates from previous studies of ~33% for lubiprostone and 17% for placebo. All tests were two-tailed with a significance level of α=0.05.

All randomized patients were analyzed for demographic and baseline disease characteristics. This population was also used to calculate the number of patients meeting the primary efficacy end point. The intent-to-treat population (all patients who took ≥1 dose of double-blind medication and had ≥1 treatment-period diary entry) was used for all other analyses of efficacy. For the primary efficacy analysis, missing data were not imputed. Weeks were calculated as 168-h intervals starting with the exact time of the first intake of study medication. If the number of hours observed was <85 for a given week, then the data were considered insufficient and the rate was missing for that week. For secondary end points, the last observation carried forward method was used to impute for weeks without SBM data.

Between-group comparisons of demographic and baseline data were made using a two-sample *t*-test (continuous variables) or χ^2-test (categorical variables). For the primary efficacy end point, groups were compared using the Cochran–Mantel–Haenszel method, stratified by pooled site. Between-group comparisons of change from baseline in SBM frequency at each week and month were made using a van Elteren test, stratified by pooled site. The proportions of patients with first SBM at 4, 8, 12, 24, and 48 h, and the median time to first SBM were calculated using the Kaplan–Meier estimates (14) and a stratified Cox proportional hazards regression model; the treatment groups were compared with a likelihood-ratio χ^2-test.

Between-group comparisons of bowel function symptoms were made using a van Elteren test stratified by pooled site. Patient HRQOL was assessed at months 1, 2, and 3 using the PAC-QOL questionnaire, which includes four subscales (dissatisfaction, physical discomfort, psychosocial discomfort, and worries and concerns) and a total score; a one-point improvement from baseline was considered clinically meaningful (12). HRQOL was further evaluated using the EQ-5D questionnaire, a descriptive system and a visual analog scale that assesses mobility, self-care, usual activities, pain and discomfort, and anxiety and depression (13). Between-group comparisons of HRQOL scores were analyzed using a van Elteren test stratified by pooled site, and then adjusted with Hommel's stagewise rejection method (15).

The incidence of TEAEs was summarized for the safety-evaluable population; comparisons of TEAE incidence were made using the Fisher exact test. To evaluate nausea, the Wilcoxon rank-sum test was used to compare the changes from baseline in FLIE results between the treatment groups. Between-group comparisons of BPI-SF scores were made using the Wilcoxon rank-sum test. Changes from baseline in opioid doses were compared between groups using a van Elteren test stratified by pooled site. Rescue medication use was compared between the treatment groups using the Cochran–Mantel–Haenszel or van Elteren test stratified by pooled site.

RESULTS

Patients

Among the 431 randomized patients, 424 received lubiprostone or placebo, and 7 received no treatment; 340 patients completed the study (**Figure 1**). Most patients were from the United States (*n*=390, 92.0%), followed by the Czech Republic (*n*=14, 3.3%), Germany (*n*=7, 1.7%), the United Kingdom (*n*=5, 1.2%), Belgium (*n*=4, 0.9%), and Poland (*n*=4, 0.9%). Most patients reported pain related to peripheral joint diseases, spinal column diseases, or skeletal and soft tissue disorders as indications for opioid therapy. On the basis of patients' recorded gastrointestinal-related medical history, 15 patients of those enrolled were known to have pre-existing constipation before initiation of opioid use. Demographic and baseline bowel function characteristics were generally similar between the two groups (**Table 1**). At baseline, the most frequently used opioid was oxycodone (18.4% of all patients), followed by hydrocodone with acetaminophen (13.9% of all patients). The observed combined mean morphine-equivalent daily dose at baseline was 99.0 mg for the placebo group and 129.9 mg for the lubiprostone group. Compliance rates were similar in the placebo (88.4%) and lubiprostone arms (90.7%; *P*=0.092). The mean (s.d.) number of days patients received a QD dose rather than a BID dose was 2.7 (7.2) for placebo and 4.5 (10.9; *P*=0.550) for lubiprostone.

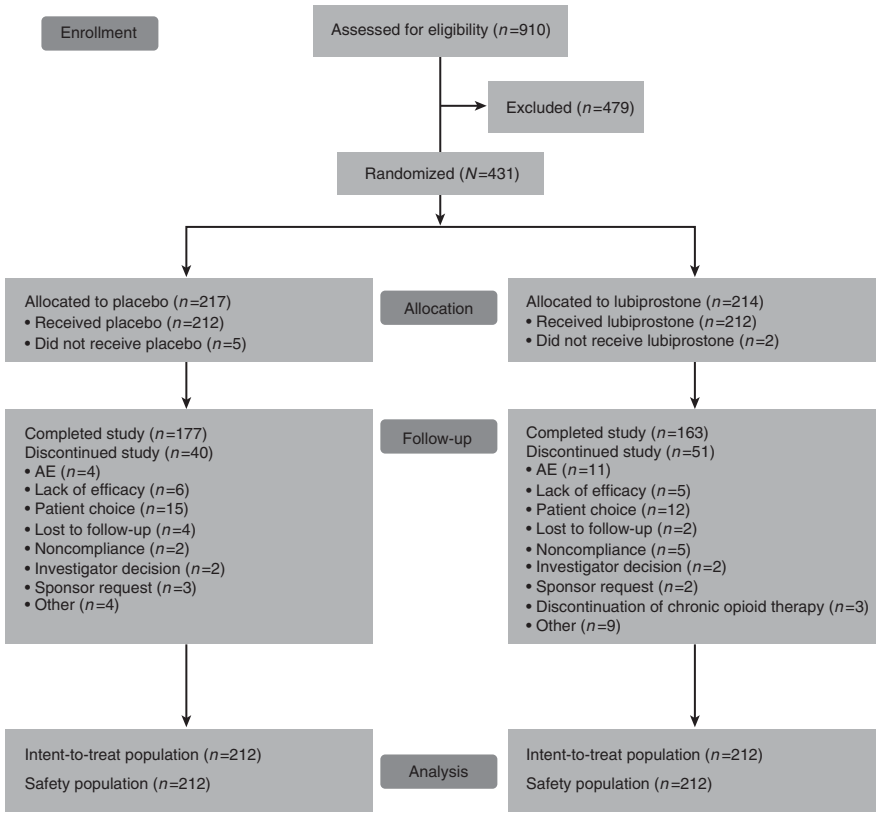

Figure 1. Patient flow diagram. AE, adverse event.

Spontaneous bowel movements

Significantly more patients in the lubiprostone group than in the placebo group were overall SBM responders (the primary end point) throughout the 12-week treatment period (27.1% [58/214] vs. 18.9% [41/217], respectively; P=0.030; **Figure 2**); the number needed to treat was 13 patients. The percentage of weekly SBM responders was significantly greater in the lubiprostone group compared with the placebo group at weeks 1 and 4 and was numerically greater at all other weeks (**Figure 2**). Furthermore, mean changes from baseline in SBM frequencies were significantly greater with lubiprostone vs. placebo overall (P=0.001) and at 9 of the 12 treatment weeks (P≤0.040; **Figure 3a**). Patients treated with lubiprostone had significantly more SBMs within 24 (P=0.008) and 48 (P=0.007) hours after the first dose relative to placebo. Median time to first SBM was significantly shorter with lubiprostone vs. placebo (23.5 vs. 37.7 h, respectively; P=0.004), with a significantly higher proportion of patients treated with lubiprostone reporting their first SBM within 4, 8, 12, 24, and 48 h of the first dose (P≤0.009; **Figure 3b**).

Secondary measures of constipation

Statistically significant improvements, although of unknown clinical significance, were observed in patients treated with lubiprostone vs. placebo in straining, stool consistency, and constipation severity (P=0.004, P<0.001, and P=0.010, respectively; **Figure 4**). Numerical differences favoring lubiprostone were observed between the treatment groups for abdominal bloating and abdominal discomfort; however, the differences did not reach statistical significance.

Health-related quality of life

Baseline PAC-QOL and EQ-5D scores were comparable for the placebo and lubiprostone treatment groups (**Supplementary Table 1** online). No significant differences were observed over the 12-week treatment period in PAC-QOL and EQ-5D measures between the placebo and lubiprostone treatment groups (**Supplementary Table 1**).

Use of rescue medication

The percentages of patients receiving lubiprostone and placebo who used rescue medication (primarily suppositories or enemas) were similar in each month of the study (P≥0.467). However, the percentage of patients who used rescue medication was consistently lower in the lubiprostone group than in the placebo group at months 1 (34.9 vs. 37.7%), 2 (23.4 vs. 26.6%), and 3 (20.5 vs. 22.0%).

Safety

The overall percentage of patients with ≥1 TEAE was similar in the placebo (49.5%; 105/212) and lubiprostone (55.2%; 117/212) groups (P=0.285; **Table 2**). Gastrointestinal TEAEs occurred in a numerically higher percentage of patients treated with lubiprostone (27.8%) than with placebo (19.3%, P=0.051). The

Table 1. Demographic and baseline bowel function characteristics of the study population for all randomized patients

Characteristic	Placebo (*n*=217)	Lubiprostone 24 μg BID (*n*=214)	*P* value
Female, *n* (%)	138 (63.6)	134 (62.6)	0.842
Mean±s.d. age, years	51.5±12.0	51.9±9.1	0.662
Race, *n* (%)			0.112
White	173 (79.7)	178 (83.2)	
African American	38 (17.5)	34 (15.9)	
Asian	1 (0.5)	1 (0.5)	
American Indian/Alaska Native	0	1 (0.5)	
Other	5 (2.3)	0	
Mean±s.d. weight, kg	*n*=212 87.0±22.1	*n*=212 86.5±23.3	0.660
Mean±s.d. MEDD, mg	*n*=212 99.0±120.3	*n*=212 129.9±226.7	0.148
Mean±s.d. SBMs per week	*n*=212 1.4±0.8	*n*=212 1.3±0.8	0.049
Mean±s.d. SBM stool consistency[a]	*n*=192 2.9±0.8	*n*=193 3.0±0.7	0.144
Mean±s.d. straining associated with SBMs[b]	*n*=192 2.6±0.8	*n*=193 2.7±0.8	0.133
Mean±s.d. abdominal discomfort/pain[b]	*n*=212 2.2±0.7	*n*=212 2.2±0.7	0.713
Mean±s.d. abdominal bloating[b]	*n*=212 2.2±0.8	*n*=212 2.2±0.7	0.435
Mean±s.d. constipation severity[b]	*n*=212 2.3±0.7	*n*=212 2.4±0.8	0.468
Mean±s.d. % of days with rescue medication use	*n*=217 7.5±11.0	*n*=214 9.5±13.5	0.392

BID, twice daily; MEDD, morphine-equivalent daily dose; SBM, spontaneous bowel movement.
[a]Scale: 0, very loose; 1, loose; 2, normal; 3, hard; 4, very hard (little balls).
[b]Scale: 0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe.

most common TEAEs in the lubiprostone group were diarrhea (11.3%), nausea (9.9%), and abdominal pain (7.1%). Diarrhea, the most common TEAE, resolved without sequelae after dose reductions. TEAE incidences in all other system organ classes were similar between the treatment groups ($P \geq 0.201$). Most patients in the placebo (93.9%; 199/212) and lubiprostone (92.0%; 195/212) groups had TEAEs of mild to moderate severity.

The percentage of patients who reported ≥1 treatment-related AE was significantly lower in the placebo group (15.1%) compared with the lubiprostone group (29.2%; $P<0.001$). However, the percentage of patients who discontinued because of an AE was low and similar in the placebo and lubiprostone groups (1.9 and 5.2%, respectively; $P=0.112$). Diarrhea, abdominal pain, nausea, and increased γ-glutamyltransferase were the most common AEs (each 1.4% of patients) leading to discontinuation of patients treated with lubiprostone.

The incidence of serious AEs was 2.8% in the placebo group and 3.3% in the lubiprostone group ($P=1.000$); only one serious AE (worsening OIC, in the placebo group) was considered treatment related. One patient died in the lubiprostone-treated group of a cause unrelated to treatment (accidental multiple drug toxicity; taking diazepam and two different formulations of hydrocodone plus acetaminophen).

There were no significant abnormalities in laboratory values, vital signs, or physical examination findings. Improvements from baseline in FLIE nausea subscale scores were similar between the lubiprostone and placebo groups. Lubiprostone did not interfere with the analgesic effects of opioids, as indicated by the BPI-SF at each month and overall: patient-reported pain severity, pain interference, and ratings of worst pain did not change substantially from baseline within either treatment group, nor were there significant differences between the treatment groups at any point. Mean changes from baseline in morphine-equivalent daily dose were similar in the lubiprostone and placebo groups at month 1 ($P=0.117$), month 2 ($P=0.853$), and month 3 ($P=0.287$).

DISCUSSION

Lubiprostone 24 μg BID for the treatment of OIC was efficacious and well tolerated among patients with chronic noncancer pain in

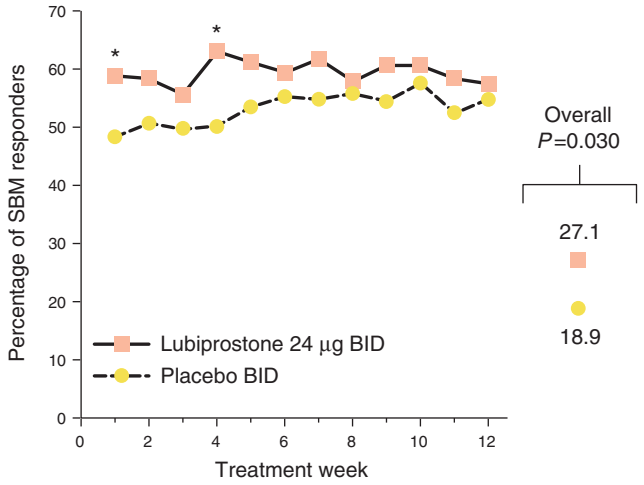

Figure 2. SBM responder rates over 12 weeks (last observation carried forward) and overall. *P<0.05, difference between the treatment groups at each week. Overall responders were defined as reporting at least moderate response (≥1 SBM improvement over baseline frequency) for all treatment weeks for which the observed data were available, as well as a full response (additional ≥3 SBMs per week) for at least 9 of the 12 treatment weeks. BID, twice daily; SBM, spontaneous bowel movement.

this randomized, double-blind, placebo-controlled study. Overall SBM response rate (the primary end point) was significantly improved for patients treated with lubiprostone compared with placebo (27.1 vs. 18.9%, respectively; P=0.030). The definition of overall SBM response required patients to record an improvement in OIC during every treatment week for which observed data were available, indicating an effect on OIC that did not diminish over time. Lubiprostone exhibited a rapid onset of effect, with significantly more patients reporting an SBM as early as 4 h after the initial dose of lubiprostone compared with placebo. This was supported by several secondary analyses, including statistically significant overall improvements in straining, stool consistency, and constipation severity during the 12-week study period. The BPI-SF domains of pain severity, pain interference, and worst pain were not significantly different from baseline, indicating that lubiprostone does not impede analgesic efficacy of the opioid. Lubiprostone displayed a safety profile that was consistent with phase 3 lubiprostone trials in patients with CIC (10,16,17). However, nausea was reported substantially less frequently than in some previous phase 3 trials (16,17), possibly because of greater emphasis on the administration of lubiprostone with meals or established tolerance of nausea (commonly associated with opioids) among the patients in this study.

Other agents that have been used to treat patients with OIC, or have been investigated for this purpose, include peripherally acting opioid antagonists (e.g., methylnaltrexone and naloxegol), prolonged-release naloxone with oxycodone, the guanylate cyclase-C agonist linaclotide, and the serotonin receptor agonist prucalopride (18,19). Of these treatments, only methylnaltrexone and naloxegol have been studied and received regulatory approval in the United States for the treatment of OIC (20,21). Methylnaltrexone must be delivered subcutaneously, unlike lubiprostone (22). In addition, gastrointestinal withdrawal responses

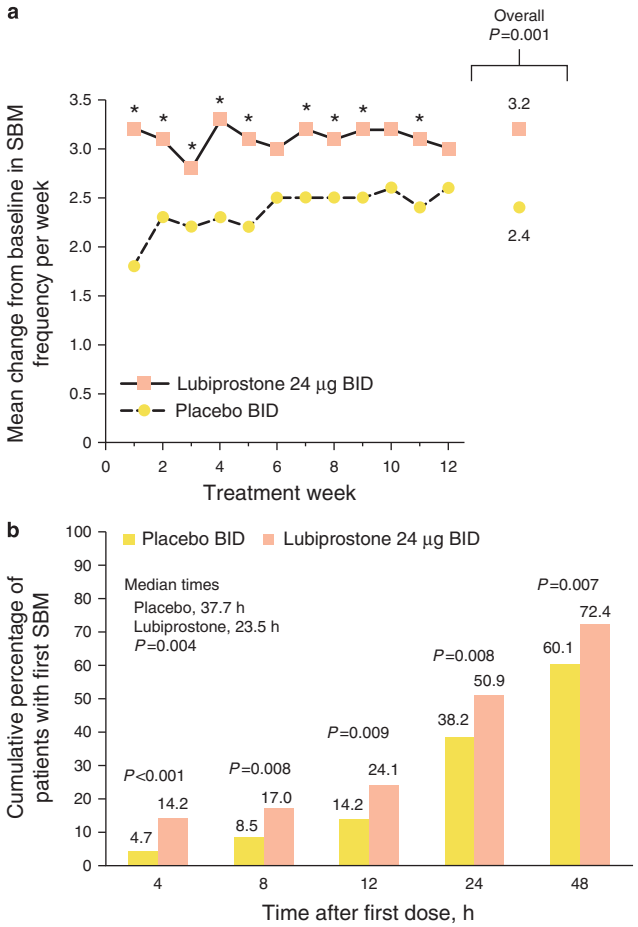

Figure 3. Improvements in SBM. (**a**) Mean change from baseline in SBM frequency over 12 weeks (last observation carried forward) and overall. *P<0.05, difference between the treatment groups at each week. (**b**) Percentage of patients with an SBM at different times after the first dose of lubiprostone 24 µg BID or matching placebo. BID, twice daily; SBM, spontaneous bowel movement.

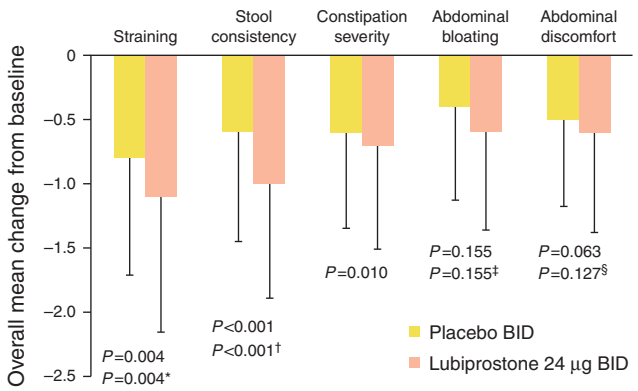

Figure 4. Overall mean change from baseline in bowel function symptoms; error bars represent s.d. Hommel's stagewise rejective method was used to adjust P values for the following: *straining, for stool consistency; †stool consistency, for straining; ‡abdominal bloating, for abdominal discomfort; and §abdominal discomfort, for abdominal bloating. The scale for stool consistency was as follows: 0, very loose; 1, loose; 2, normal; 3, hard; 4, very hard (little balls). The scale for other measures was as follows: 0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe. BID, twice daily.

Table 2. TEAEs (safety population)

Patients, *n* (%)	Placebo (*n*=212)	Lubiprostone 24 μg BID (*n*=212)	*P* value
≥1 TEAE[a]	105 (49.5)	117 (55.2)	0.285
Gastrointestinal disorders	41 (19.3)	59 (27.8)	0.051
Diarrhea	8 (3.8)	24 (11.3)	
Nausea	10 (4.7)	21 (9.9)	
Vomiting	11 (5.2)	9 (4.2)	
Abdominal pain	0	15 (7.1)	
≥1 Treatment-related AE[b]	32 (15.1)	62 (29.2)	<0.001
Gastrointestinal disorders	22 (10.4)	49 (23.1)	<0.001
Diarrhea	3 (1.4)	21 (9.9)	
Nausea	6 (2.8)	18 (8.5)	
Abdominal pain	0	12 (5.7)	
Flatulence	5 (2.4)	6 (2.8)	
Vomiting	3 (1.4)	6 (2.8)	

AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event.
[a]Incidences of individual TEAEs observed in ≥5% of patients in either treatment group.
[b]Incidences of individual treatment-related AEs observed in ≥2% of patients in either treatment group.

characterized by abdominal cramping can be evoked by peripheral opioid antagonists (23), whereas lubiprostone is mechanistically incapable of inducing central or gastrointestinal opioid withdrawal (18). A combination formulation consisting of prolonged-release naloxone with oxycodone has been shown to provide analgesic efficacy and improve bowel function in patients with chronic noncancer pain (24); however, this medication is not available in the United States. Alvimopan is an opioid antagonist that is indicated for short-term use (up to 7 days) following surgeries that include partial bowel resection with primary anastomosis (25). Linaclotide is indicated for the treatment of patients with CIC and irritable bowel syndrome with constipation, but has not yet been studied for the treatment of OIC (26). Prucalopride is unavailable in the United States and is no longer in development for the treatment of patients with OIC (27).

One limitation of the present study may be the exclusion of patients treated with diphenylheptane opioids. Patients taking methadone and propoxyphene were excluded because nonclinical studies have shown that diphenylheptane opioids may dose-dependently reduce the effects of lubiprostone by interfering with the activation of ClC-2 chloride channels (28). Patients taking mixed partial opioid antagonists/agonists (e.g., buprenorphine) were also excluded to avoid potentially confounding gastrointestinal effects due to opioid receptor antagonism. In addition, although patients may have taken laxatives or stool softeners before study enrollment, response to previous therapies was not recorded at screening, and there was no requirement for a trial period of conservative therapy before randomization.

In the present study, lubiprostone demonstrated efficacy over a 12-week period; however, a 36-week extension of two other phase 3 studies has confirmed the safety and effectiveness of lubiprostone in patients with OIC (29). In a long-term (48-week) open-label study among patients with CIC, lubiprostone was well tolerated and it consistently improved bowel symptoms (30). Results were similar in another long-term study (up to 52 weeks) among patients with irritable bowel syndrome with constipation (31).

In conclusion, considering lubiprostone's significant overall response rates, tolerable AE profile, and oral delivery route, it presents a viable option for patients with chronic noncancer-related pain who experience OIC as a consequence of opioid therapy.

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CONFLICT OF INTEREST

Guarantor of the article: M. Mazen Jamal, MD, MPH.
Specific author contributions: M.M.J. was the lead principal investigator, enrolled patients in the study, and contributed to the manuscript development. A.B.A., J.-P.J. and L.R.W. enrolled patients in the study and contributed to manuscript development. All authors approved the submission of the final version.
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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Constipation has been estimated to affect 15–80% of patients with chronic noncancer pain treated with opioids and negatively impacts their health-related quality of life.
- ✓ Opioid-induced constipation involves infrequent and incomplete bowel movements, straining, and hard, dry stool consistency.
- ✓ Lubiprostone was recently FDA-approved and is currently the only therapy indicated for opioid-induced constipation resulting from chronic opioid treatment for noncancer pain.

WHAT IS NEW HERE

- ✓ Oral lubiprostone significantly improved opioid-induced constipation and related symptoms in adults with chronic noncancer-related pain.
- ✓ Significant improvements with lubiprostone vs. placebo included spontaneous bowel movements, straining, stool consistency, and constipation severity.
- ✓ Oral lubiprostone was well tolerated and did not result in opioid withdrawal symptoms; no serious adverse events were assessed as treatment-related.

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