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*Original Research Article*

# Efficacy of Lubiprostone for the Treatment of Opioid-Induced Constipation, Analyzed by Opioid Class

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## Abstract

**Objectives. To examine the efficacy and safety of lubiprostone for the treatment of opioid-induced constipation (OIC) in patients by opioid class received.**

**Design. Data were pooled from three phase III, randomized, double-blind, placebo-controlled studies.**

**Subjects/Setting. Adults with chronic noncancer pain receiving opioid therapy for 30 or more days and diagnosed with OIC.**

**Methods. Overall mean change from baseline in spontaneous bowel movement (SBM) frequency, overall treatment response (≥1 SBM/week improvement over baseline SBM frequency in all treatment weeks with available data and ≥3 SBMs/week for ≥9 of the 12 weeks of treatment), and OIC-related symptoms were examined in patients taking opioids. Data were pooled and analyzed by opioid group.**

**Results. In patients receiving phenanthrene opioids (e.g., oxycodone; N = 1,159), lubiprostone significantly increased overall mean changes in SBM frequency from baseline ($P = 0.0001$), increased overall response rate ($P = 0.0024$), and improved OIC symptoms ($P \leq 0.0229$) vs placebo. Patients receiving phenylpiperidine opioids (e.g., fentanyl; N = 137) had significant improvement in SBM frequency ($P = 0.0129$) and favorable trends in response rates (21.4% vs 9.8%; $P = 0.0723$) and OIC symptoms vs placebo. Efficacy was not observed in**

**overall analyses of patients receiving diphenylheptane opioids (e.g., methadone), although an increase in SBM frequency was observed in patients who received a morphine-equivalent daily dose of 200 or fewer mg, suggesting a dose-dependent negative interference of this opioid class on lubiprostone effects. For all groups, the lubiprostone adverse event profile was similar; the most common treatment-emergent adverse events were nausea and diarrhea.**

**Conclusions. In patients using commonly prescribed opioids, lubiprostone is effective and generally well tolerated for the treatment of OIC.**

**Key Words. Chronic Pain; Opioids; Hydrocodone; Methadone; Morphine; Oxycodone**

## Introduction

Patients receiving opioids to manage chronic pain commonly experience opioid-induced constipation (OIC) [1], which is characterized by infrequent and incomplete bowel movements, hard stool, straining, and abdominal pain and bloating [2]. Opioids cause constipation in the gastrointestinal tract by delaying gastric transit, reducing secretions, and increasing fluid reuptake [2,3]. OIC can add to the overall disease burden in patients with chronic pain. It is reported to be the most bothersome side effect of opioid therapy and negatively affects quality of life. Approximately one-third of patients have reported decreasing their use of opioid therapies (e.g., by missing or reducing doses) in an attempt to manage constipation; these efforts, however, resulted in increased levels of pain [4].

The US Food and Drug Administration (FDA) approved lubiprostone (24 mcg twice daily [BID]) in 2006 for the treatment of chronic idiopathic constipation, and it approved lubiprostone in 2013 for the treatment of OIC in adults with chronic noncancer pain [5]. Lubiprostone enhances intestinal fluid secretion by local and selective activation of type 2 chloride channels (ClC-2) on the apical membrane of the intestinal epithelium, thereby increasing the liquidity of the intestinal contents [6,7]. This mechanism of action is distinct from other OIC treatments, such as peripherally acting μ-opioid receptor antagonists [8]. Because lubiprostone does not interact with opioid receptors, it bypasses opioid antisecretory actions in the gastrointestinal tract and does not interfere with analgesia [8,9].

The efficacy and tolerability of lubiprostone for the treatment of OIC was demonstrated in three randomized, controlled clinical trials [10,11]. However, the effectiveness of lubiprostone for the treatment of OIC for specific opioid classes and subclasses has not been well studied. Results from two initial phase III studies suggested the possibility of a decrease in the efficacy of lubiprostone in patients using diphenylheptane opioids (e.g., methadone) [12]. A subsequent in vitro study demonstrated that methadone inhibited the effects of lubiprostone on ClC-2 chloride channels in a dose-dependent manner [13]. As a result of these preclinical and clinical findings, patients receiving diphenylheptane opioids were excluded in a third phase III study [11].

To provide clinically relevant information regarding the use of lubiprostone with various opioids, to inform rotation in the management of opioid tolerance and adverse events (AEs), and to better understand the efficacy and safety of lubiprostone, a pooled analysis of patients receiving various classes of opioids during the three phase III studies of lubiprostone for OIC is reported herein. Efficacy also was analyzed in three subpopulations grouped by subclasses of phenanthrene opioids—morphine or codeine, hydrocodone or oxycodone, and hydromorphone or oxymorphone—to further characterize the effectiveness of lubiprostone within this opioid class. Finally, data from patients who received diphenylheptane opioids (primarily methadone) in two of the three studies enabled a closer examination of the dose effects of diphenylheptane opioids on lubiprostone efficacy.

## Methods

### *Study Design*

Data were pooled from three similarly designed randomized, double-blind, placebo-controlled, phase III pivotal efficacy studies (Study 1, NCT01298219 [11]; Study 2, NCT00595946 [10]; Study 3, NCT00597428 [14]). In each study, patients were randomized 1:1 to receive lubiprostone 24 mcg BID or matching placebo BID for 12 weeks, after a three-week screening period.

The study protocol and amendments, informed consent forms, advertisements, and other information given to the patients and/or their guardians were reviewed and approved before use by the institutional review board (IRB) for each study center. All patients signed the IRB-approved informed consent forms before enrollment. All studies were conducted in compliance with the US Code of Federal Regulations, the ethical principles of the Declaration of Helsinki, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

### *Patients*

All three studies had similar inclusion and exclusion criteria. Participants were adults age 18 years or older who were receiving opioid therapy for 30 or more days for chronic, non-cancer-related pain and had been diagnosed with OIC. OIC was defined as an average of fewer than three spontaneous bowel movements (SBMs) per week during the screening period and one of more of the following OIC-related symptoms for 25%

or more of their SBMs during each week of the screening period: hard or very hard stool, sensation of incomplete evacuation, and moderate to very severe straining. An SBM was defined as a bowel movement that occurred during the previous 24-hour period without use of laxatives or stool softeners.

From the screening visit until study completion, discontinuation of any medications that could affect gastrointestinal motility (other than opioid therapy) was required. Under certain protocol-defined circumstances, investigators were allowed to prescribe short-term use of rescue medications with limited effect duration (e.g., bisacodyl suppository) for the immediate relief of constipation.

Patients were excluded if opioid treatment was modified by a ±30% change in morphine-equivalent daily dose (MEDD), route, or agent within 30 days of screening or if they were likely to have a dose adjustment or treatment discontinuation during the study. Patients who had bowel disorders (i.e., obstructions, ulcerative colitis, or Crohn's disease), who had had gastrointestinal or abdominal surgery within 90 days of screening, who had had a bowel resection at any time, or who had constipation that was judged by the investigator as not resulting from opioid use or related to secondary causes (i.e., malnutrition, spinal cord disorders, hypothyroidism, diabetes) were excluded. In Study 1, patients receiving opioids in the diphenylheptane class were excluded.

*Efficacy Outcomes*

Efficacy outcomes examined in this analysis were 1) overall change from baseline in SBM frequency; 2) overall treatment response, which was defined as an increase of one or more SBMs per week from baseline (in all treatment weeks for which data were available) and three or more SBMs per week for nine or more of the 12 weeks of treatment; and 3) patient-reported assessments of straining, stool consistency, constipation severity, abdominal bloating, and abdominal pain. Straining, constipation severity, abdominal bloating, and abdominal pain were recorded daily by patients using the following scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). Stool consistency was rated as 0 (very loose), 1 (loose), 2 (normal), 3 (hard), or 4 (very hard).

*Safety*

Adverse events (AEs) were recorded from the first dose of study medication until the follow-up visit two weeks after the last dose and coded using the Medical Dictionary for Regulatory Activities, version 13.1 (http://www.meddra.org).

*Statistical Analysis*

Data were pooled and analyzed by phenanthrene, phenylpiperidine, or diphenylheptane opioid class (Table 1). Data from patients taking phenanthrene and phenylpiperidine opioids concurrently were included in both groups. Data from patients taking diphenylheptane opioids either alone or concurrent with phenanthrenes and/or phenylpiperidines were included in the diphenylheptane class. Efficacy was also examined in a diphenylheptane-only group, which excluded patients taking concurrent phenanthrenes and/or phenylpiperidines, and in three patient subpopulations receiving subclasses of phenanthrene opioids: morphine or codeine, hydrocodone or oxycodone, and hydromorphone or oxymorphone. Patients taking phenanthrene opioids from more than one subgroup were included in all appropriate subpopulations.

**Table 1** Chemical classes of opioid drugs*

| | | |
|---|---|---|
| Phenanthrenes | Buprenorphine | Levorphanol |
| | Butorphanol | Morphine |
| | Codeine | Nalbuphine |
| | Heroin | Naloxone |
| | Hydrocodone | Oxycodone |
| | Hydromorphone | Oxymorphone |
| Phenylpiperidines | Fentanyl | Remifentanil |
| | Meperidine | Sufentanil |
| Diphenylheptanes | Methadone | Propoxyphene |

*Opioids of the benzomorphan class were not used in the lubiprostone opioid-induced constipation studies.

Statistical differences between treatment groups in patient demographics and baseline characteristics were determined by Fisher's exact test for categorical variables and by *t* test for continuous variables. Statistical differences in baseline gastrointestinal symptoms were determined using the van Elteren test, stratified by study for the pooled groups. Efficacy analyses were conducted in randomized patients who received one or more doses of medication and provided one or more treatment-period diary entries (intent-to-treat population). For efficacy assessments, patients who received study treatment other than their randomization assignment were included in their originally assigned randomization group. Safety analyses included all randomized patients who took one or more doses of double-blind medication. For safety assessments, patients who received a study treatment other than their randomization assignment were included in the group for the treatment actually received. The observed case analysis was used, and no missing values were imputed. Data from patients who did not have the assessments at a specific week visit were excluded from the analysis.

Statistical significance for overall change in SBM frequency from baseline was determined by the van Elteren test, stratified by pooled center. Overall responder rates were compared using the Cochran-Mantel-Haenszel test with clinical site as a stratification factor. Treatment effects in the overall change from baseline for OIC-related symptoms were assessed using

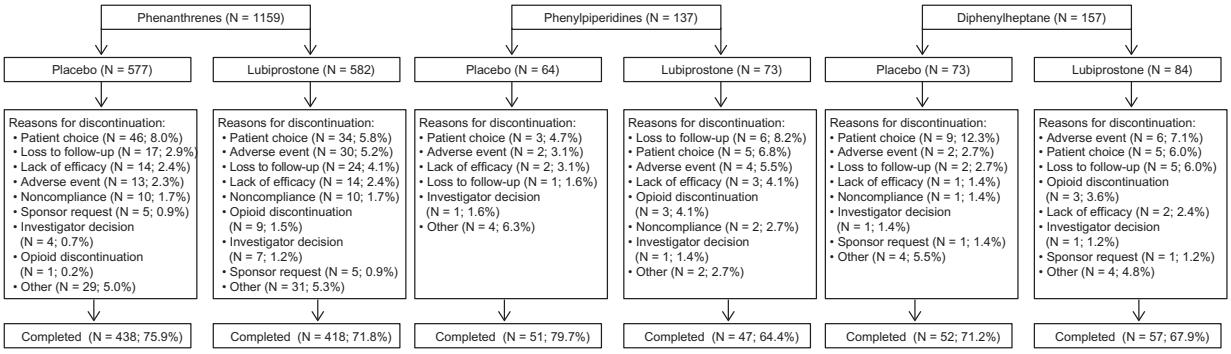


**Figure 1** Patient* disposition by opioid class. *Patients entering treatment; intent-to-treat population. Patients who took both phenanthrene and phenylpiperidine opioids were counted in each group.

the van Elteren test, stratified by pooled center. All statistical significance was determined at the 0.05 level.

Regression analysis was used to evaluate the relationship between diphenylheptane MEDD (mg) and overall SBM frequency rates for patients receiving diphenylheptane opioids at 450 or fewer mg.

## Results

### *Patient Disposition*

A total of 1,159 patients received phenanthrene opioids (alone or concurrent with phenylpiperidines), 137 received phenylpiperidine opioids (alone or concurrent with phenanthrenes), and 157 patients received diphenylheptane opioids (alone or concurrent with phenylpiperidines and/or phenanthrenes) (Figure 1). Completion rates were generally similar when stratified by opioid class and treatment assignment (range = 64.4–79.7%). Among all groupings, the most common reasons for study discontinuation were patient choice (range = 4.7–12.3%), adverse events (range = 2.3–7.1%), loss to follow-up (range = 1.6–8.2%), and other (range = 2.7–6.3%). Notably, the discontinuation rates for lack of efficacy in all lubiprostone groups were low (range = 2.4–4.1%) and comparable with the rates in the corresponding placebo groups (range = 1.4–3.1%).

### *Demographic and Baseline Characteristic*

Demographics and characteristics at baseline were generally similar for the lubiprostone and placebo groups when stratified by opioid class (Table 2). In the phenylpiperidine group, there were statistically significant differences in mean age, with a higher mean age in the lubiprostone vs placebo group. For all groups, there was a similar burden of disease at baseline based on mean SBMs per week (mean = 1.3, SD = 0.9, to mean = 1.6, SD = 0.8) and symptom scores for straining, stool consistency, constipation severity, abdominal bloating, and abdominal pain.

### *Efficacy by Opioid Class*

Compared with placebo, lubiprostone treatment significantly increased overall SBM frequency from baseline in patients with OIC receiving phenanthrene or phenylpiperidine opioids ($P = 0.0001$ and $P = 0.0129$, respectively), but not in patients receiving diphenylheptane opioids ($P = 0.585$). Further, no efficacy with lubiprostone vs placebo was observed in a subset of patients receiving diphenylheptanes only ($P = 0.0917$) (Figure 2A). Similar effects were found in the analysis of overall responder rates. In patients who used phenanthrene opioids, significantly higher response rates were seen with lubiprostone treatment compared with placebo (24.4% vs 16.9%; $P = 0.0024$) (Figure 2B). Although a similar response rate was observed in the phenylpiperidine opioid group in patients receiving lubiprostone vs placebo (21.4% vs 9.8%), the difference did not reach statistical significance ($P = 0.0723$); however, there was a lower number of patients in this group. Patients receiving diphenylheptane opioids in combination with other opioid classes had numerically higher but nonsignificant response rates with lubiprostone compared with placebo ($P = 0.6425$). The subset of patients who received diphenylheptanes had a numerically higher but nonsignificant overall response rate with placebo compared with lubiprostone ($P = 0.1956$).

Statistically significant improvements from baseline in all OIC-related symptoms were observed in patients receiving phenanthrene opioids with lubiprostone treatment compared with placebo ($P \leq 0.0229$) (Figure 3A). In the phenylpiperidine opioid group, there was a favorable but nonsignificant trend for improvement in OIC-associated symptoms with lubiprostone (Figure 3B). Among patients in the diphenylheptane and diphenylheptane-only groups, there were no significant differences between lubiprostone treatment and placebo; however, small numerical differences favoring lubiprostone were observed, particularly in the diphenylheptane-only group (Figure 3, C and D).

**Table 2** Patient demographic and baseline characteristics by opioid class, intent-to-treat population

| | Phenanthrene (N = 1,159) | | Phenylpiperidine (N = 137) | | Diphenylheptane (N = 157) | |
|---|---|---|---|---|---|---|
| | Placebo (N = 577) | Lubiprostone (N = 582) | Placebo (N = 64) | Lubiprostone (N = 73) | Placebo (N = 73) | Lubiprostone (N = 84) |
| Sex, No. (%) | | | | | | |
| Female | 359 (62.2) | 367 (63.1) | 43 (67.2) | 47 (64.4) | 45 (61.6) | 49 (58.3) |
| Male | 218 (37.8) | 215 (36.9) | 21 (32.8) | 26 (35.6) | 28 (38.4) | 35 (41.7) |
| Mean age (SD), y | 50.3 (11.3) | 50.5 (9.7) | 48.5 (8.5) | 51.9 (9.3)* | 50.3 (12.1) | 47.8 (8.9) |
| Age group, No. (%), y | | | | | | |
| ≥18 to < 65 | 518 (89.8) | 539 (92.6) | 60 (93.8) | 66 (90.4) | 67 (91.8) | 83 (98.8) |
| ≥65 | 59 (10.2) | 43 (7.4) | 4 (6.3) | 7 (9.6) | 6 (8.2) | 1 (1.2) |
| Race, No. (%) | | | | | | |
| White | 474 (82.1) | 475 (81.6) | 60 (93.8) | 68 (93.2) | 66 (90.4) | 70 (83.3) |
| Black | 81 (14.0) | 89 (15.3) | 1 (1.6) | 5 (6.8) | 6 (8.2) | 9 (10.7) |
| Asian | 4 (0.7) | 5 (0.9) | 0 | 0 | 1 (1.4) | 0 |
| American Indian or Alaska Native | 5 (0.9) | 6 (1.0) | 1 (1.6) | 0 | 0 | 4 (4.8) |
| Other/unknown | 13 (2.3) | 7 (1.2) | 2 (3.1) | 0 | 0 | 1 (1.2) |
| MEDD,† No. | 573 | 579 | 63 | 72 | 73 | 84 |
| Mean (SD), mg | 191.1 (330.5) | 205.5 (440.1) | 409.4 (457.8) | 421.3 (517.1) | 712.9 (700.5) | 831.9 (1,168.7) |
| Median (range), mg | 90.0 (4.5–3,100.0) | 90.0 (4.0–7,605.0) | 292.0 (16.5–2,772.0) | 297.8 (7.5–3,268.5) | 450.0 (23.1–3,656.3) | 457.5 (22.5–7,605.0) |
| MEDD† group, No. (%), mg | | | | | | |
| <200 | 424 (73.6) | 411 (70.6) | 18 (28.6) | 24 (32.9) | 15 (20.5) | 10 (11.9) |
| ≥200 | 149 (25.9) | 168 (28.9) | 45 (71.4) | 48 (65.8) | 58 (79.5) | 74 (88.1) |
| Unknown | 3 (0.5) | 3 (0.5) | 0 | 1 (1.4) | 0 | 0 |
| SBM frequency, No. | 571 | 569 | 63 | 72 | 73 | 83 |
| Mean (SD) SBMs/wk | 1.5 (1.1) | 1.4 (1.1) | 1.4 (1.0) | 1.2 (0.9) | 1.6 (0.8) | 1.4 (1.0) |
| Straining,‡ No. | 505 | 501 | 55 | 58 | 68 | 74§ |
| Mean (SD) | 2.6 (0.8) | 2.7 (0.9) | 2.7 (0.8) | 2.7 (1.0) | 2.8 (0.8) | 2.7 (0.9) |
| Stool consistency,‡ No. | 505 | 501 | 55 | 58 | 68 | 74 |
| Mean (SD) | 2.9 (0.8) | 3.0 (0.8) | 3.0 (0.9) | 3.0 (0.9) | 3.3 (0.6) | 2.9 (0.8) |
| Constipation severity,‡ No. | 577 | 579 | 64 | 73 | 73 | 84 |
| Mean (SD) | 2.3 (0.7) | 2.4 (0.8) | 2.3 (0.8) | 2.3 (0.8) | 2.3 (0.7) | 2.4 (0.8) |
| Abdominal bloating,‡ No. | 577 | 579 | 64 | 73 | 73 | 84 |
| Mean (SD) | 2.2 (0.8) | 2.2 (0.8) | 2.2 (0.8) | 2.1 (0.8) | 2.1 (0.8) | 2.3 (0.8) |
| Abdominal pain,‡ No. | 577 | 579 | 64 | 73 | 73 | 84 |
| Mean (SD) | 2.1 (0.7) | 2.2 (0.7) | 2.1 (0.7) | 2.0 (0.7) | 2.1 (0.7) | 2.2 (0.8) |

MEDD = morphine-equivalent daily dose; SBM = spontaneous bowel movement.
*$P \leq 0.05$ vs placebo, based on Fisher's exact test for categorical variables and the *t* test for continuous variables.
†For 30 or more days of screening.
‡Straining, constipation severity, abdominal bloating, and abdominal pain were rated by the patient as 0 (absent), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). Stool consistency was rated by the patient as 0 (very loose), 1 (loose), 2 (normal), 3 (hard), or 4 (very hard).
§$P = 0.002$ vs placebo, based on the van Elteren test, stratified by study for the pooled groups.

*Efficacy by Subgroups of Phenanthrene Opioids*

In analysis of the overall change from baseline in SBM frequency by phenanthrene opioid subclasses, patients receiving hydrocodone or oxycodone had a significant increase in SBM frequency ($P = 0.0002$) and improvements in all OIC-related symptoms with lubiprostone vs placebo ($P \leq 0.01120$) (Figures 4 and 5A). Of note, these agents comprised the largest proportion of all agents received in the total analyzed population (75.3%; 960/1,275).

Improvements in SBM frequency from baseline were demonstrated with lubiprostone treatment in the other

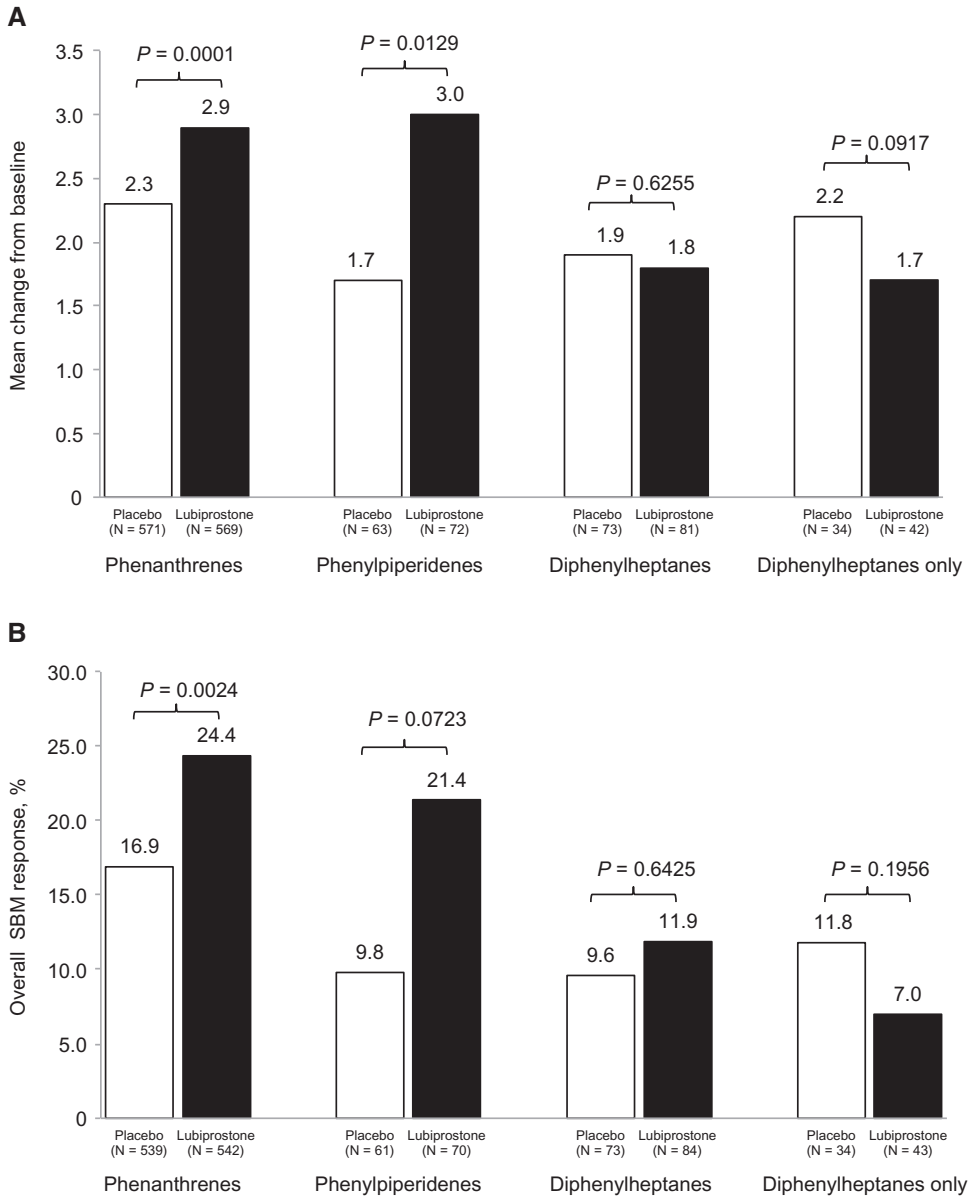


**Figure 2** Lubiprostone treatment compared with placebo by opioid class in **(A)** overall mean change from baseline in SBM frequency and **(B)** overall response rates. *P* values for overall mean change from baseline in SBM frequency from van Elteren tests stratified by pooled center. *P* values for overall response rates based on Cochran-Mantel-Haenszel test. A positive overall treatment response was defined as an increase of one or more SBMs per week from baseline (in all treatment weeks for which data were available) and three or more SBMs per week for nine or more of the 12 weeks of treatment. SBM = spontaneous bowel movement.

phenanthrene opioid subpopulations (the morphine or codeine group and the hydromorphone or oxymorphone group), although statistically significant differences with lubiprostone vs placebo were not reached in either group (Figure 4). The magnitude of change and difference from placebo in mean SBM changes from baseline for the hydromorphone or oxymorphone and the hydrocodone or oxycodone subgroup with lubiprostone were comparable (3.2 and 3.0, respectively; 0.6 difference from placebo for both), even though statistical significance was not identified in the former group. Similar findings were observed for changes from baseline for OIC-related symptoms in patients receiving hydromorphone or oxymorphone (Figure 5B). Compared with placebo, lubiprostone treatment produced decreases in all OIC-related symptom assessments, and the magnitude

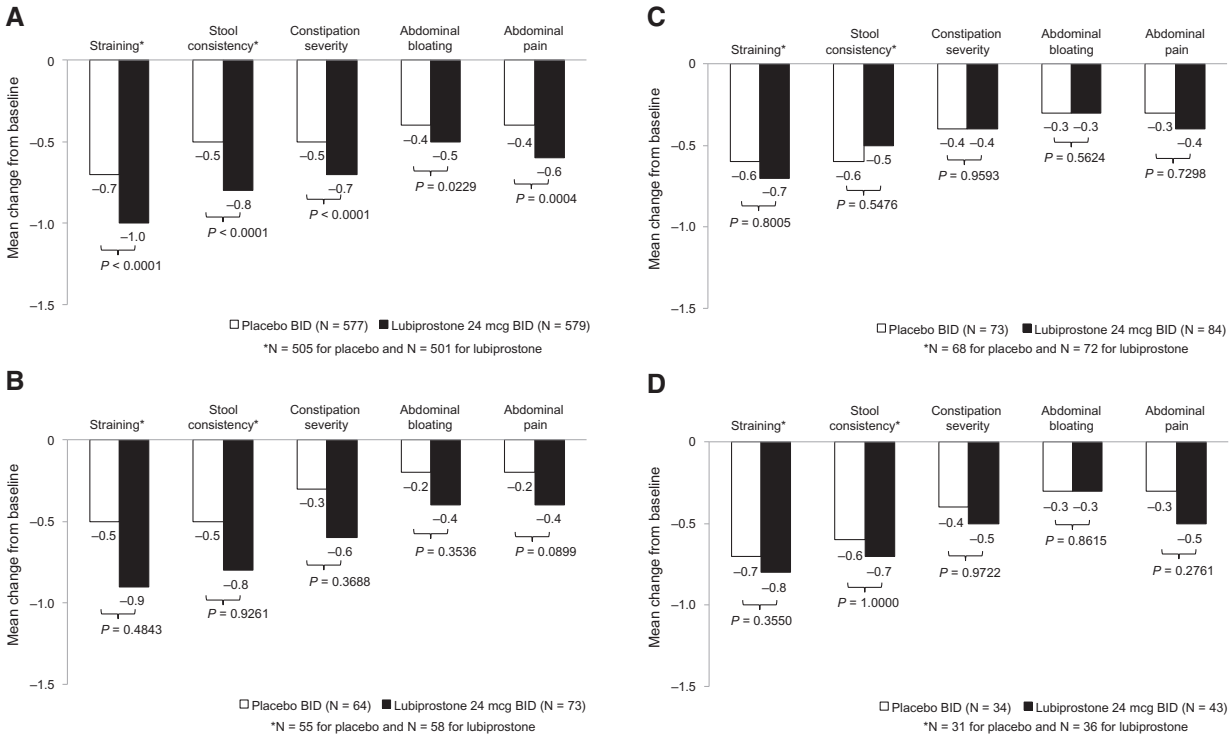


**Figure 3** Overall mean change from baseline in OIC-related symptom scores by opioid class: **(A)** phenanthrene, **(B)** phenylpiperidine, **(C)** diphenylheptanes, and **(D)** diphenylhepatanes only. *P* values from van Elteren tests, stratified by pooled center. Straining, constipation severity, abdominal bloating, and abdominal pain were rated by the patient as 0 (absent), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). Stool consistency was rated by the patient as 0 (very loose), 1 (loose), 2 (normal), 3 (hard), or 4 (very hard). BID = twice daily; OIC = opioid-induced constipation.

of the mean changes from baseline were comparable with those observed for the hydrocodone or oxycodone subgroup. However, only differences in constipation severity and abdominal pain were statistically significant with lubiprostone in patients using hydromorphone or oxymorphone ($P = 0.0045$ and $P = 0.0104$, respectively). In these statistical analyses, relatively low sample sizes for the hydromorphone or oxymorphone group ($\leq$70 patients in total) were observed. Patients receiving morphine or codeine reported decreases in some OIC-associated symptoms, with statistically significant differences in straining and stool consistency ($P = 0.0291$ and $P = 0.0409$, respectively) (Figure 5C).

### *Efficacy of Lubiprostone by Morphine-Equivalent Daily Dose in Patients Receiving Methadone*

The effect of opioid dose on SBM frequency was assessed in patients taking 450 or fewer mg MEDD of diphenylheptane opioids (N = 49), using data from Studies 2 and 3, which included patients receiving diphenylheptane opioids. Demographic data and disease status parameters at baseline for this subpopulation were consistent with the other analyzed populations (data not shown). At baseline, the mean SBM frequency was 1.2 (SD = 0.9) per week for the 26 patients from Study 2 and 1.7 (SD = 0.98) per week for the 23 patients in Study 3. Regression analysis demonstrated that there was a dose-dependent negative relationship ($r^2$=0.1668) between diphenylheptane MEDDs and overall SBM frequency (Figure 6).

### *Safety*

The numbers of patients reporting any treatment-emergent AEs (TEAEs) were similar in both the lubiprostone and placebo treatment groups for all opioid classes ($P \geq 0.125$) (Table 3). Gastrointestinal TEAEs occurred more frequently in patients receiving lubiprostone vs placebo in the phenanthrene (30.9% vs 20.7%; $P < 0.001$) and diphenylheptane (31.8% vs 13.9%; $P = 0.013$) opioid groups but not in the phenylpiperidine opioid group (37.5% vs 30.8%; $P = 0.472$). The most commonly reported TEAEs in the lubiprostone treatment groups were nausea (13.4%–18.1%), diarrhea (1.2%–13.9%), and abdominal pain (4.7%–5.6%). In the population overall, the greatest likelihood of experiencing the first episode of any of these three TEAEs was greatest in the first week of treatment and decreased thereafter.

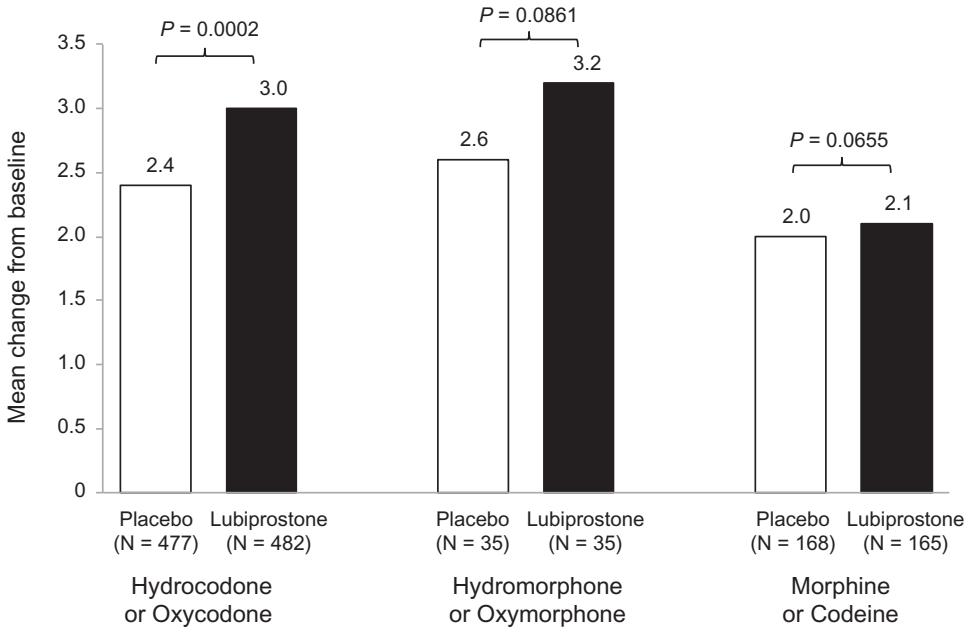


**Figure 4** Overall mean change from baseline in frequency of spontaneous bowel movements in subpopulations grouped by phenanthrene opioid subclasses. *P* values from van Elteren tests, stratified by pooled center.

## Discussion

This analysis by opioid class demonstrated the efficacy of lubiprostone in patients receiving phenanthrene opioids (e.g., morphine, oxycodone), which were received by 91% of patients in the pooled population. Significant improvements with lubiprostone vs placebo were observed in overall mean change from baseline in SBM frequency, the overall responder rate, and in all OIC-associated symptoms. For patients receiving phenylpiperidine opioids (e.g., fentanyl, meperidine), statistical significance with lubiprostone vs placebo was found in some efficacy measures only. However, the overall magnitude of positive effects with lubiprostone compared with placebo suggest that the lack of statistical significance is likely due to small patient numbers in this subgroup. Individual clinical trials were not powered to evaluate response in subgroups defined by opioid class.

The use of the phenanthrene opioids hydrocodone or oxycodone was highly prevalent in the analyzed population, with 75% of patients overall receiving one or the other of these agents. Statistically significant improvements in the overall mean change from baseline in SBM frequency and all OIC symptoms were observed in this subgroup with lubiprostone compared with placebo. Although statistical significance with lubiprostone was only found in some efficacy measures for patients receiving hydromorphone or oxymorphone, the overall magnitude of the effects vs placebo again suggest that small patient numbers account for the lack of statistical significance. For reasons that are unclear, a statistically significant increase in SBM frequency was not observed with lubiprostone compared with placebo in patients receiving morphine or codeine. Baseline SBM frequencies were similar in all of the phenanthrene subgroup populations, so baseline SBM frequency could not account for the efficacy differences observed in these subpopulations at week 12. The end points of straining and stool consistency were significantly improved in patients taking morphine or codeine; these aspects are of at least as much importance to patients with OIC as SBM frequency [4].

Consistent with results identified in in vitro cell assays demonstrating that methadone dose-dependently reduced the activation of ClC-2 by lubiprostone [13], no clear efficacy was demonstrated in patients receiving diphenylheptane opioids (e.g., methadone). It appears that lubiprostone may improve SBM frequency at lower doses of diphenylheptanes ($\leq$200 mg MEDD), but higher doses of diphenylheptane opioids appear to interfere with the effects of lubiprostone. The limitations regarding the efficacy of lubiprostone in patients receiving diphenylheptane opioids are consistent with the current prescribing information [5]. It should be noted, however, that methadone comprises a small percentage of all opioid prescriptions based on prescription surveillance data from eight states in the United States (~2%) [15].

An analysis of AEs demonstrated a similar tolerability profile for lubiprostone in all opioid classes. AE rates (overall and by type) were consistent with those previously reported in the individual studies [10,11], and no new safety signals were noted in our analyses. Because of the unique mechanism of action of lubiprostone,

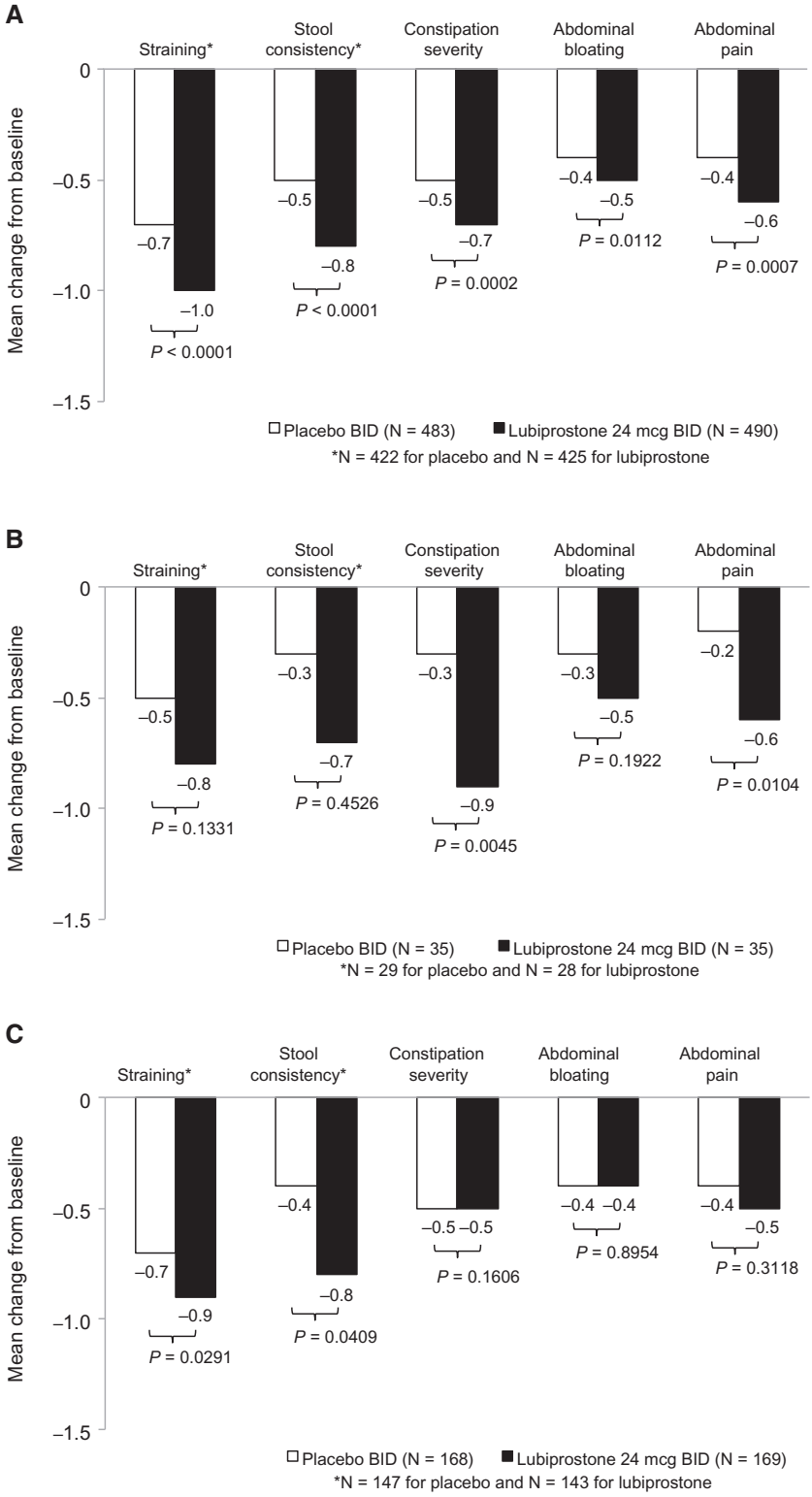


**Figure 5** Overall mean change from baseline in OIC-related symptom scores in subpopulations grouped by phenanthrene opioid subclasses: **(A)** hydrocodone or oxycodone; **(B)** hydromorphone or oxymorphone; **(C)** morphine or codeine. *P* values from van Elteren tests stratified by pooled center. Straining, constipation severity, abdominal bloating, and abdominal pain were rated by the patient as 0 (absent), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). Stool consistency was rated by the patient as 0 (very loose), 1 (loose), 2 (normal), 3 (hard), or 4 (very hard). BID = twice daily; OIC = opioid-induced constipation.

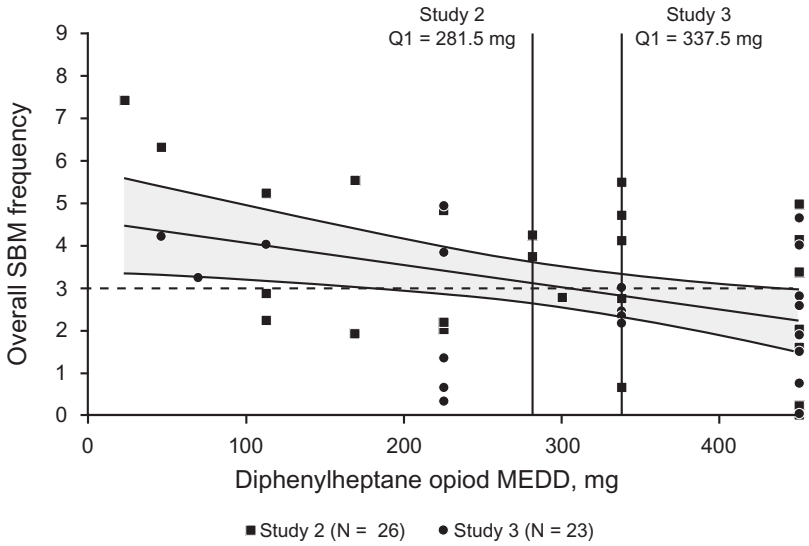


**Figure 6** Regression analysis of the relationship between overall SBM frequency and diphenylheptane dose in patients receiving 450 or fewer mg MEDD of diphenylheptane opioids in Studies 2 and 3. The gray shaded area represents the 95% confidence interval. MEDD = morphine-equivalent daily dose; Q1 = first quartile of diphenylheptane MEDD; SBM = spontaneous bowel movement.

**Table 3** Treatment-emergent adverse events by opioid class occurring in ≥5% of patients in any group; safety population

| | Phenanthrenes (N = 1,162) | | | Phenylpiperidines (N = 137) | | | Diphenylheptanes (N = 157) | | |
|---|---|---|---|---|---|---|---|---|---|
| TEAE, No. (%) | Placebo (N = 580) | Lubiprostone (N = 582) | *P** | Placebo (N = 65) | Lubiprostone (N = 72) | *P** | Placebo (N = 72) | Lubiprostone (N = 85) | *P** |
| Any | 305 (52.6) | 333 (57.2) | 0.125 | 41 (63.1) | 45 (62.5) | 1.000 | 42 (58.3) | 49 (57.6) | 1.000 |
| Any GI disorder† | 120 (20.7) | 180 (30.9) | <0.001 | 20 (30.8) | 27 (37.5) | 0.472 | 10 (13.9) | 27 (31.8) | 0.013 |
| TEAE type‡ | | | | | | | | | |
| Nausea | 37 (6.4) | 78 (13.4) | | 6 (9.2) | 13 (18.1) | | 7 (9.7) | 13 (15.3) | |
| Diarrhea | 24 (4.1) | 61 (10.5) | | 5 (7.7) | 10 (13.9) | | 1 (1.4) | 1 (1.2) | |
| Vomiting | 23 (4.0) | 22 (3.8) | | 0 | 2 (2.8) | | 2 (2.8) | 5 (5.9) | |
| Flatulence | 17 (2.9) | 24 (4.1) | | 4 (6.2) | 3 (4.2) | | 1 (1.4) | 6 (7.1) | |
| Abdominal pain upper | 15 (2.6) | 5 (0.9) | | 6 (9.2) | 0 | | 0 | 1 (1.2) | |
| Headache | 13 (2.2) | 15 (2.6) | | 0 | 4 (5.6) | | 2 (2.8) | 2 (2.4) | |
| Abdominal distension | 12 (2.1) | 25 (4.3) | | 2 (3.1) | 4 (5.6) | | 1 (1.4) | 5 (5.9) | |
| Abdominal pain | 7 (1.2) | 31 (5.3) | | 3 (4.6) | 4 (5.6) | | 3 (4.2) | 4 (4.7) | |
| Edema peripheral | 6 (1.0) | 14 (2.4) | | 0 | 1 (1.4) | | 1 (1.4) | 5 (5.9) | |
| Gastroenteritis | 2 (0.3) | 7 (1.2) | | 0 | 4 (5.6) | | 0 | 1 (1.2) | |

GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities, version 13.1; TEAE = treatment-emergent adverse event.

*Difference between lubiprostone and placebo using Fisher's exact test.

†By MedDRA System Organ Class.

‡By MedDRA Preferred Term.

negative effects associated with peripheral opioid receptor antagonists, such as increased incidence of abdominal pain [16] or opioid withdrawal (a precaution in the prescribing information for the two peripheral opioid receptor antagonists that have received FDA approval for the treatment of OIC [17,18]) should not be a concern. In

pain assessment analyses using individual and pooled lubiprostone clinical trial data, no interference with opioid analgesia was demonstrated [9].

A limitation of the current analysis includes the relatively small sample sizes for some opioid groups (i.e., phenylpiperidines) and subgroups (i.e., hydromorphone or oxymorphone), which may preclude a full understanding of the effects of lubiprostone treatment in patients using these agents.

In conclusion, our findings suggest that lubiprostone treatment provides significant improvements in OIC for patients receiving treatment from the opioid classes and subclasses most commonly prescribed in clinical practice [15,19], with a generally similar efficacy and tolerability profile across opioid classes. Consistent with previously reported preclinical and clinical findings, diphenylheptanes appear to interfere with the clinical activity of lubiprostone [12,13]. However, results from the current study suggest that some activity of lubiprostone may be retained with lower doses of diphenylheptanes, although formal demonstration of the effects is lacking.

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