

Lubiprostone for the Treatment of Functional Constipation in Children

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See “Lubiprostone in Pediatric Functional Constipation” by Faure on page 275.

ABSTRACT

Objectives: Pediatric functional constipation is common; effective, easily administered treatment options are limited. Lubiprostone is an oral chloride channel protein-2 activator that stimulates gastrointestinal fluid secretion, softens stools, and facilitates bowel movements (BMs). We evaluated the safety and effectiveness of lubiprostone in children and adolescents with functional constipation.

Methods: Patients ≥ 12 kg, 17 years or younger, and with < 3 spontaneous BMs (SBMs; ie, BMs that did not occur within 24 hours of rescue medication use) per week were enrolled at 22 US general pediatric and pediatric gastroenterology centers (January 2007–October 2008). Patients received 4 weeks of open-label lubiprostone at doses of 12 μg once daily (QD), 12 μg twice daily (BID), or 24 μg BID based on age and weight. The primary endpoint was SBM frequency during week 1 versus baseline.

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Results: Of 127 enrolled patients, 124 were treated and analyzed (12 μg QD, $n = 27$; 12 μg BID, $n = 65$; 24 μg BID, $n = 32$), and 109 completed the study. The mean age of treated patients was 10.2 years (range 3–17 years); 65 were boys. Mean SBM frequency significantly increased compared with baseline at week 1 (3.1 vs 1.5 SBMs/week, $P < 0.0001$). SBM frequency was improved significantly from baseline overall ($P < 0.0001$) and for individual dose groups ($P \leq 0.0062$) during weeks 2, 3, and 4. Common ($\geq 5\%$) adverse events included nausea (18.5%), vomiting (12.1%), diarrhea (8.1%), abdominal pain (7.3%), and headache (5.6%). Two patients experienced serious adverse events (unrelated abdominal pain; unrelated sickle cell crisis).

Conclusions: Lubiprostone was efficacious and well tolerated in children and adolescents with functional constipation.

Key Words: bowel movement, children, constipation, lubiprostone, pediatric

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The prevalence of functional constipation among children in the general population ranges from approximately 1% to 30% (1). Symptoms of constipation include abdominal distention, infrequent bowel movements (BMs), hard stools, and painful evacuations (2,3). Children who experience painful BMs may avoid defecation as long as possible, thereby exacerbating the constipation-associated symptoms. Present guidelines (4) for the treatment of childhood constipation recommend a number of agents for disimpaction and relief of constipation, including polyethylene glycol (PEG), other osmotic laxatives (eg, lactulose), lubricants (eg, mineral oil), stimulant laxatives, and enemas; however, some of these agents may be challenging to administer to children (5), and a meta-analysis revealed that only 61% of treated children fully recovered from constipation by 6 to 12 months after presentation (6). Furthermore, prolonged use of stimulant laxatives is often not recommended in children with constipation because of the possibility of permanent gut, muscle, or nerve damage (4). With the removal of tegaserod, cisapride, and phenolphthalein from the armamentarium (7–9), pharmaceutical options for the treatment of pediatric constipation have become more limited. Surgical interventions may be effective but are reserved for those with demonstrated severe colonic dysmotility and may be inappropriate for most children with functional constipation (10), whereas techniques such as transcutaneous electrical stimulation are not yet established therapies (11). Thus, effective treatment alternatives are needed to provide symptomatic relief in children and adolescents with functional constipation.

Lubiprostone (Amitiza, Sucampo Pharma Americas, Bethesda, MD; and Takeda Pharmaceuticals, Deerfield, IL) is a prostone that, acting locally as a specific activator of chloride channel protein-2 in the gastrointestinal epithelium, promotes intestinal secretion of chloride ions and fluid, and enhances gastrointestinal motility and the occurrence of BMs (12,13). Lubiprostone is approved in the United States for the treatment of chronic idiopathic constipation in adults, opioid-induced constipation in adults with

chronic, noncancer pain, and irritable bowel syndrome with constipation in adult women (14). Double-blind randomized placebo-controlled trials demonstrated that lubiprostone was generally well tolerated and provided symptomatic relief when given for 3 to 4 weeks to adults with chronic idiopathic constipation (15–17). The efficacy of lubiprostone in adults and the similarity of many of the symptoms associated with constipation in adults and children suggest that the drug may provide relief of constipation-associated symptoms in children; however, no studies have been conducted to provide evidence on whether lubiprostone is safe and effective for the treatment of functional constipation in pediatric patients. The objective of this open-label study was to evaluate the safety and effectiveness of lubiprostone in children with functional constipation, including a limited exploration of different doses and posologies to guide future randomized, well-controlled clinical trials.

METHODS

Patients

Patients ages 17 years or younger, ≥ 12 kg in weight, capable of swallowing capsules without chewing, and who met the Rome III diagnostic criteria for functional constipation (18), were eligible for enrollment in the study. The Rome III criteria define functional constipation as ≥ 2 of the following in a child ≥ 4 developmental years without irritable bowel syndrome: ≤ 2 defecations in the toilet per week; ≥ 1 episode of fecal incontinence per week; history of retentive posturing or excessive volitional stool retention; history of painful or hard BMs; presence of large fecal mass in the rectum; and history of large-diameter stool that may obstruct the toilet (18). Patients were excluded if they had constipation attributable to secondary causes (eg, dietary, physical, neurologic, or organic factors), Hirschsprung disease, nonretentive fecal incontinence, fecal impaction that required manual disimpaction at screening or baseline (before enrollment), uncontrolled systemic disease (including cardiovascular, liver, or lung disease, neurologic or psychiatric disorder, or other systemic disease), renal impairment, or cancer within the past 5 years. Sexually active patients were required to use contraception; pregnant or nursing female patients were excluded. Patients who previously received lubiprostone or participated in another trial within 30 days of screening were excluded.

During a 2-week baseline period, patients reported BM frequency and consistency using electronic diaries. A spontaneous BM (SBM) was defined as any BM that did not occur within 24 hours following the use of a rescue medication. Eligible patients must have experienced < 3 SBMs per week on average during baseline. Eligible patients must also have experienced any of the following during baseline: an SBM with straining, a hard SBM, or no SBM during the baseline period. At the conclusion of the baseline period, patients were reassessed to ensure that they continued to meet the eligibility requirements defined by the inclusion and exclusion criteria.

Study Design

This prospective, multicenter, open-label, safety and effectiveness study involved an initial 2-week baseline period, a 4-week open-label treatment period, and a 2-week follow-up period. Patients were recruited from 22 general pediatric and pediatric gastroenterology centers throughout the United States. The study was conducted in accordance with Title 21 of the US Code of Federal Regulations, Good Clinical Practice, consistent with the Declaration of Helsinki and the International Conference on Harmonisation (19). The study protocol and informed consent form were approved before use by the institutional review board of each participating center. Each patient and/or 1 parent or guardian provided written informed consent before enrollment and initiation of the study.

Study Treatments

Patients who met eligibility requirements at baseline were enrolled. Lubiprostone was provided in 12- and 24- μ g capsules. Using body weight, an appropriate dose of lubiprostone in pediatric patients was extrapolated using the US Centers for Disease Control and Prevention clinical growth chart (20) and allometric scaling of the approved dose of lubiprostone (24 μ g twice daily [BID]) for relief of chronic idiopathic constipation in adults. The clinical growth chart indicates that approximately 95% of US adults reach a weight ranging from 53 to 93 kg (males) or 45 to 81 kg (females); thus, the daily adult dosage of lubiprostone for constipation ranges from a minimum of 0.5 to 0.6 μ g/kg to a maximum of 0.9 to 1.1 μ g/kg. The following 3 doses were calculated for pediatric patients in this study: young children (younger than 6 years) who weighed ≥ 12 kg received 12 μ g once daily (QD); older children (6–11 years of age) received 12 μ g QD if they weighed 12 to < 24 kg, 12 μ g BID if they weighed 24 to < 36 kg, and 24 μ g BID if they weighed ≥ 36 kg; adolescents (12–17 years of age) received 12 μ g BID (up to 24 patients) or, after a protocol amendment, 24 μ g BID if they weighed ≥ 36 kg. A subsequent amendment to the study protocol during the trial changed the lubiprostone dose assignment from 12 μ g BID to 24 μ g BID for patients with body weight ≥ 36 kg. Thus, patients with body weight ≥ 36 kg received 12 μ g BID only if they participated early during the trial, before the protocol amendment. The first dose of lubiprostone was taken at the clinic following consumption of a meal, and all patients were instructed to take subsequent doses of study drug with food and at least 8 ounces of water. Lubiprostone dosing could be reduced from BID to QD or, in the case of patients assigned the 12- μ g QD dose, dosing could be withheld for up to 3 days, at the discretion of the investigator in response to nausea, diarrhea, or other adverse events (AEs).

Patients using a daily fiber supplement at a stable dose and schedule for ≥ 1 month before the baseline period were permitted to continue that regimen throughout the study. Investigators documented patient use of medications (prescribed, over the counter, herbal and/or supplemental) within 90 days of baseline, and patients could continue their use throughout the study, with the exception of the following agents to be discontinued ≥ 2 weeks before baseline: cholinesterase inhibitors, anticholinergics, antispasmodics, anti-diarrheals, prokinetics, laxative agents (including PEG), and any other medications known to affect symptoms of constipation. Patients taking a stable dose of medication to treat attention-deficit/hyperactivity disorder for ≥ 1 month before baseline were permitted to use that drug at the same dose and schedule of administration throughout the study.

Rescue medications, which could be administered at the discretion of the investigator if a BM had not occurred within a 3-day period, included Dulcolax (bisacodyl, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) suppositories and tablets, Fleet Enema (dibasic sodium phosphate and monobasic sodium phosphate, C.B. Fleet Company, Lynchburg, VA), and Senokot (senna, Purdue Pharma Products, Stamford, CT). If the recommended rescue medication failed, another medication could be prescribed. Patients were instructed not to take rescue medication for ≤ 24 hours before the first dose of lubiprostone and for 1 week thereafter.

Assessments of Effectiveness

Patients ages 12 to 17 years and guardians of patients younger than 12 years were instructed on the daily use of electronic diaries to record study drug administration, use of any rescue medications, occurrence of BMs, stool consistency, fecal incontinence, straining and pain associated with BMs, constipation

severity, abdominal symptoms (bloating and discomfort) associated with constipation, and treatment effectiveness.

The primary effectiveness outcome was the frequency of SBMs during week 1 compared with baseline. A power analysis showed that a sample size of 120 patients had 90% power to detect a mean change of 1.5 SBMs at week 1 with a standard deviation of 5 SBMs and a type I error rate of 0.05.

Secondary effectiveness outcomes included weekly patient-reported SBM frequency (ie, other than the assessment at week 1), frequency of SBMs in the toilet, BM frequency, percentage of patients with SBMs within 24 and 48 hours of the first dose of lubiprostone, and time to first SBM following the first dose of lubiprostone. Weekly responder rates, frequency of fecal incontinence, the average degree of straining associated with SBMs, stool consistency of SBMs, painful SBMs, abdominal bloating, abdominal discomfort, constipation severity, and treatment effectiveness were also assessed. Severity of constipation, abdominal bloating, abdominal discomfort, painful BMs, and bowel straining were rated using a 5-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe. Treatment effectiveness was rated on a 5-point scale from 0 (not at all effective) to 4 (extremely effective). Ratings of stool consistency were assessed using the 7-point Bristol Stool Form Scale (1 [separate hard lumps like nuts] to 7 [watery, no solid pieces]) in pictorial format (21). The language of diary questions could be modified for age appropriateness using emoticons based on the Wong-Baker Faces Pain Rating Scale to represent severity scale codes (eg, 0–4) and descriptions of symptoms (22). Designated emoticons were provided in the study protocol and were consistent across study sites. Nonresponders (<3 SBMs/week, withdrawal because of lack of effectiveness, or use of rescue medication during a given week or within 24 hours before that week) were distinguished from moderate responders (3 SBMs/week) and full responders (≥ 4 SBMs/week).

Safety Assessments

Investigators assessed safety at the screening visit, 2 weeks later at the baseline visit, at subsequent clinic visits at weeks 1, 4, and 6, and by telephone at weeks 2 and 3. Investigators recorded patient-reported AEs and determined their severity (mild, moderate, or severe) and relation to lubiprostone treatment (unrelated or possibly, probably, or definitely related). Investigators also determined which AEs were serious, defined as an event that was fatal, life-threatening, permanently disabling, prompted or prolonged inpatient hospitalization, was a congenital anomaly, or was otherwise medically important in the investigator's opinion. Clinical laboratory tests, measurement of vital signs, and physical examinations were performed at clinic visits.

Statistical Analysis

All patients who received ≥ 1 dose of lubiprostone and had ≥ 1 diary entry during the treatment period (the intent-to-treat [ITT] population) were included in the analysis of effectiveness, and all patients who received ≥ 1 dose of lubiprostone were included in the safety analysis. Patient demographics and baseline disease characteristics were summarized using descriptive statistics. Assessment of the statistical significance of the change from baseline in the primary outcome was performed using the Wilcoxon signed-rank test. Secondary outcomes were summarized weekly by dose level and overall with last observations carried forward to replace missing data. The time to onset of the first SBM following the first dose of lubiprostone was analyzed using Kaplan-Meier estimates. The percentage of patients with SBMs within 24 and 48 hours of the

first dose of lubiprostone was summarized using descriptive statistics. The patient-reported outcomes of stool consistency, bowel straining, and painful BM were summarized, and the change from baseline was evaluated with a 1-sample *t* test or Wilcoxon signed-rank test. All *P* values were 2-sided at a significance level of $\alpha = 0.05$. The number and percentage of responders at each week were summarized by dose level and overall (ie, for the entire population). Treatment-emergent AEs were coded by system organ class and preferred term; incidences were summarized by dose and overall.

RESULTS

Patients

Of the 127 patients enrolled in the study (Fig. 1), 109 (85.8%) completed the trial, which was conducted from January 23, 2007 to October 28, 2008. Overall, the most common reasons for discontinuation were AEs (6.3%; 8/127) and voluntary withdrawal (3.9%; 5/127). Three patients withdrew from the study before administration of the first dose of lubiprostone. The ITT and safety analysis populations included 123 and 124 patients, respectively. One patient who took a dose was excluded from the ITT population because no diary entries were recorded. Within the ITT population, the 12- μg QD dose group included young children (younger than 6 years) with a body weight ≥ 12 kg ($n = 15$) and older children (6–11 years of age) with a body weight of 12 to <24 kg ($n = 12$). The 12- μg BID dose group included older children with a body weight of 12 to <24 kg ($n = 1$), 24 to <36 kg ($n = 27$), and ≥ 36 kg ($n = 15$), and adolescents ($n = 22$, of which 20 had a body weight ≥ 36 kg at baseline). The 24- μg BID dose group included older children ($n = 6$) and adolescents ($n = 25$) with a body weight ≥ 36 kg. The patient who was included only in the safety population was 16 years of age and received the 24- μg BID dose. Most patients (83.9%; 104/124) were compliant with lubiprostone treatment (ie, took 80%–120% of expected doses); 13.7% of patients (17/124) took <80% of assigned doses, and 0.8% of patients (1/124) took >120%.

Baseline demographic characteristics are summarized in Table 1. Patients ranged in age from 3 to 17 years. Most patients were white (>75% in each treatment arm); most patients in the lubiprostone 12- μg QD and BID treatment arms were boys, but most patients in the lubiprostone 24- μg BID arm were girls. Baseline symptoms were balanced across the study arms and consistent with the entry criteria that were intended to select patients with functional constipation. Concomitant medications, including rescue medications, taken by >10% of patients were PEG (43.5%; 54/124), bisacodyl (11.3%; 14/124), loratadine (11.3%; 14/124), ibuprofen (10.5%; 13/124), paracetamol (ie, acetaminophen; 10.5%; 13/124), and salbutamol (ie, albuterol; 10.5%; 13/124).

SBMs

For the primary endpoint of mean SBM frequency at week 1, the ITT population exhibited a statistically significant increase compared with baseline (3.1 vs 1.5, $P < 0.0001$; Fig. 2A). Each of the 3 dose groups also exhibited improvements in week 1 SBM frequencies compared with baseline (Fig. 2B–D), reaching statistical significance for the 12- μg BID and 24- μg BID groups but not the 12- μg QD group; however, children in the 12- μg QD arm younger than 6 years showed a statistically significant improvement in SBM frequency at week 1 compared with baseline (3.3 vs 1.5, $P = 0.0254$). The greatest improvement in SBM frequency at week 1 compared with baseline (3.8 vs 1.6, $P < 0.0001$) was observed in the lubiprostone 24- μg BID group (Fig. 2D).

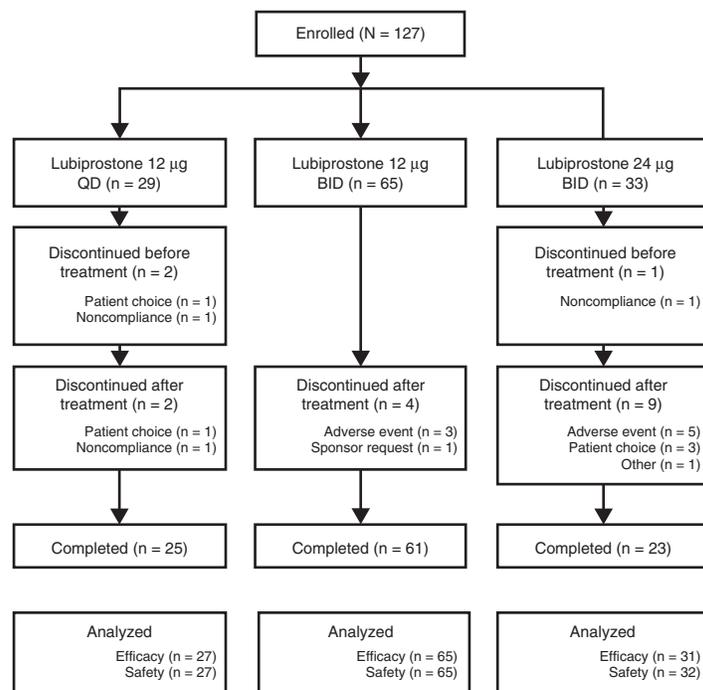


FIGURE 1. Patient disposition. BID = twice daily; QD = once daily.

For the secondary endpoints of SBM frequency at weeks 2, 3, and 4, we observed statistically significant improvements compared with baseline at every time point for the overall ITT population (Fig. 2A) and for each of the 3 dose groups (Fig. 2B–D). Changes from baseline SBM frequency in the toilet and BM frequency followed patterns similar to those for the effectiveness endpoints already described (Supplemental Digital Content 1 and 2, <http://links.lww.com/MPG/A261>). In the overall ITT population, the frequency of fecal incontinence was significantly reduced from baseline (mean \pm standard deviation, 1.7 ± 3.6 episodes/week) only at week 3 ($P = 0.0056$). Statistically significant decreases in incontinence also occurred in the 12- μ g BID group at weeks 3 and 4 ($P \leq 0.0189$).

Time to Onset of Treatment Effect

Approximately one-third of patients (35.0%; 43/123) experienced an SBM within 24 hours of the first dose of lubiprostone; the onset of effect at 24 hours occurred more often with the 24- μ g BID dose than with the 12- μ g QD and 12- μ g BID doses (Fig. 3). The majority of patients (61.8%; 76/123) experienced an SBM within 48 hours of the first dose of lubiprostone; onset at 48 hours was least common with the 12- μ g QD dose, followed by the 12- μ g BID dose, and most common with the 24- μ g BID dose.

Responder Status

In the overall ITT population, $\geq 43\%$ of patients achieved a moderate or full response to treatment at all time points after baseline (Fig. 4). The greatest overall response (50.8%; 62/122) was observed at week 1. Patients assigned to the lubiprostone 24- μ g BID group exhibited the greatest response in most individual weeks compared with patients in the 12- μ g QD and 12- μ g BID groups.

Constipation-Associated Symptoms

The subjective measures of constipation-associated symptoms and treatment effectiveness recorded in patient diaries are shown in Figure 5. Baseline values for straining, stool consistency, and painful SBMs were comparable across all treatment arms; the overall ITT population exhibited statistically significant improvements in all of these symptoms at weeks 1 to 4 compared with baseline ($P \leq 0.0192$). Patients in individual dose groups exhibited statistically significant improvement at weeks 1 to 4 in straining and painful SBMs at nearly all time points after baseline, whereas statistically significant improvements in stool consistency at each time point from weeks 1 to 4 were achieved only in the lubiprostone 24- μ g BID group. There were trends for improvement in abdominal bloating, abdominal discomfort, and severity of constipation during the 4-week treatment, although abdominal discomfort was stable in the 12- μ g QD group. Mean patient ratings of treatment effectiveness during weeks 1 to 4 ranged from 1.5 to 1.9 in the overall ITT population and from 1.2 to 2.0 among the individual dose groups; these values corresponded to ratings of ‘‘a little bit’’ to ‘‘moderately’’ effective.

Use of Rescue Medication

During the 2-week baseline period, 29.0% of patients (36/124) used rescue medications. The percentage of patients using rescue medications overall decreased to 9.7% during week 1 (during which time patients were to avoid use of such medications) and then ranged from 13.7% to 21.8% of patients during weeks 2 to 4.

Safety

Overall, 65.3% of patients (81/124) experienced ≥ 1 AE during the study (Table 2). Most patients (96.3%; 78/81) who

TABLE 1. Demographics and disease status at baseline (safety population)

Demographics	Lubiprostone 12 µg QD, n = 27	Lubiprostone 12 µg BID, n = 65	Lubiprostone 24 µg BID, n = 32
Age, y			
Mean ± SD	5.5 ± 1.7	10.3 ± 2.8	13.9 ± 3.0
Median (range)	5 (3–9)	10 (6–17)	14 (6–17)
Body weight, kg			
Mean ± SD	19.9 ± 2.8	43.4 ± 18.0	60.0 ± 16.9
Median (range)	19.3 (14.4–25.0)	36.6 (22.1–101.9)	57.3 (36.0–99.0)
Sex, n (%)			
Male	15 (55.6)	41 (63.1)	9 (28.1)
Female	12 (44.4)	24 (36.9)	23 (71.9)
Race, n (%)			
White	26 (96.3)	51 (78.5)	26 (81.3)
Black or African American	1 (3.7)	9 (13.8)	5 (15.6)
Asian	0	1 (1.5)	0
Other	0	4 (6.2)	1 (3.1)
Disease status, mean ± SD			
No. SBMs/wk	1.5 ± 0.8	1.4 ± 0.8	1.6 ± 1.0
No. BMs/wk	1.7 ± 0.7	1.7 ± 0.9	1.0 ± 1.1
No. fecal incontinence episodes/wk	3.3 ± 2.2	1.8 ± 1.1	0.1 ± 0.1
Consistency of SBM*	2.8 ± 1.2	3.0 ± 1.4	2.6 ± 1.2
Straining associated with SBM†	1.9 ± 0.8	1.6 ± 0.9	2.1 ± 0.9
Pain associated with SBM†	1.7 ± 0.9	1.4 ± 1.0	1.5 ± 1.0

BID = twice daily; BM = bowel movement; QD = once daily; SBM = spontaneous bowel movement.

* Assessed on the 7-point Bristol Stool Form Scale (1 = separate hard lumps like nuts to 7 = watery, no solid pieces) (21).

† Assessed on a 5-point scale (0 = none to 4 = very severe).

reported AEs experienced no severe events. Three patients reported severe AEs (pyrexia, n = 2 [12-µg QD group], not treatment related; upper abdominal pain, n = 1 [12-µg BID group], possibly treatment related). The incidence of AEs was higher (78.1%; 25/32) in the lubiprostone 24-µg BID group than in the other dose groups.

There was no relation between the dose of lubiprostone and any AE, with the exception of nausea, which occurred in 31.3% (10/32) of patients taking lubiprostone 24 µg BID compared with 18.5% (12/65) taking lubiprostone 12 µg BID and 3.7% (1/27) taking lubiprostone 12 µg QD. Typically, AEs of nausea began soon after

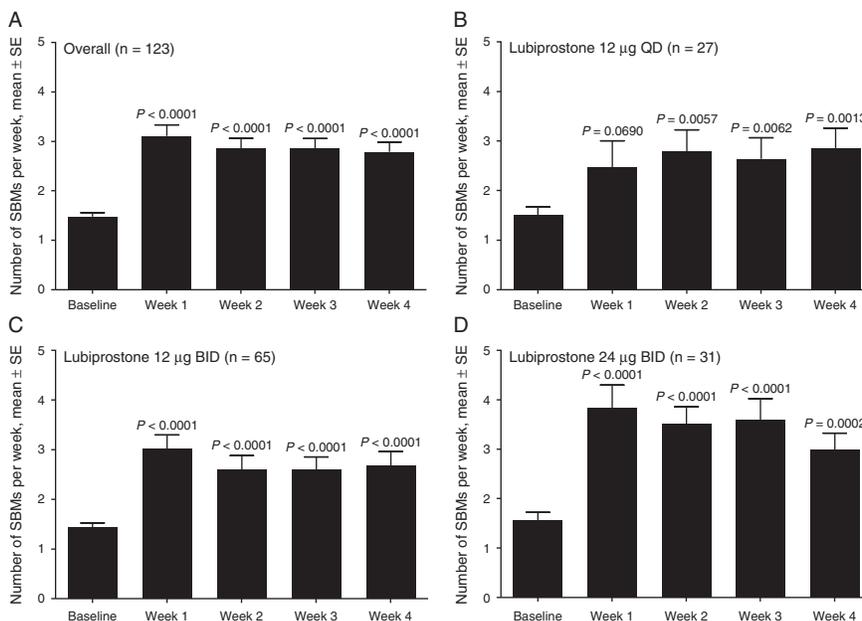


FIGURE 2. Frequency of SBMs overall (A) and in each dose group (B–D) following treatment with lubiprostone compared with baseline (ITT population). BID = twice daily; ITT = intent to treat; QD = once daily; SBM = spontaneous bowel movement. P values from Wilcoxon signed-rank test for mean change from baseline.

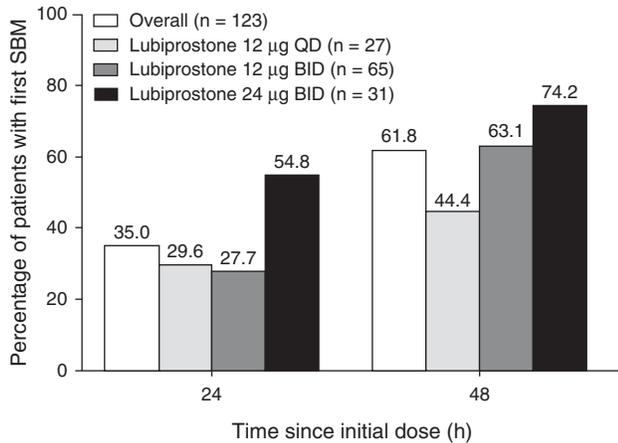


FIGURE 3. Onset of first SBM following treatment with lubiprostone (ITT population). BID = twice daily; ITT = intent to treat; QD = once daily; SBM = spontaneous bowel movement.

treatment initiation (median onset, day 2) and resolved soon afterwards (median duration, 2.5 days). One patient experienced multiple AEs of nausea (2 consecutive events, each lasting 1 day). The AEs that investigators most often considered at least possibly related to lubiprostone included nausea, vomiting, and diarrhea. Overall, 26.6% (33/124) of patients had at least 1 gastrointestinal AE possibly related to lubiprostone; these events were mild or moderate in all but the 1 patient, taking lubiprostone 12 µg BID, who experienced a severe AE of upper abdominal pain, considered possibly related to treatment. Two other patients, both taking lubiprostone 12 µg QD, experienced severe AEs of pyrexia, considered unrelated to treatment.

Overall, 6.5% (8/124) of patients withdrew from the study because of an AE, including nausea (n = 3; 2 definitely related, 1 probably related), acute respiratory distress (n = 1; probably related), celiac disease (n = 1; unlikely related), upper abdominal pain caused by fecal mass (n = 1; unlikely related), vomiting (n = 1; probably related), and weight loss (n = 1; possibly related). AEs that led to study discontinuation were mild or moderate in severity. Five of 124 patients (4.0%) required a reduction in lubiprostone dose because of AEs; these AEs were mild or moderate and considered probably (n = 4) or unlikely (n = 1) related to lubiprostone. There were no clinically significant trends in clinical laboratory tests, vital signs, or physical examinations. There were 2 serious AEs (abdominal pain and sickle cell anemia with crisis), both reported in the lubiprostone 12-µg BID group and considered by the investigators to be unrelated to lubiprostone. There were no deaths during the study.

DISCUSSION

Previous studies demonstrated that lubiprostone provided effective symptomatic relief and was well tolerated in adults with chronic idiopathic constipation (15–17). The primary objective of this open-label study was to assess the safety and effectiveness of lubiprostone in children and adolescents with functional constipation in relation to the safety and efficacy data available for adults with chronic idiopathic constipation. Results showed that lubiprostone treatment was associated with statistically significant improvements in SBM frequency after just 1 week of treatment and for up to 3 additional weeks in children and adolescents. Lubiprostone was well tolerated in enrolled patients. Lubiprostone, whose mechanism of action is distinct from those of other available agents, may be appropriate to fill the unmet need for new treatments when standard therapies fail to resolve symptoms of functional constipation in children and adolescents.

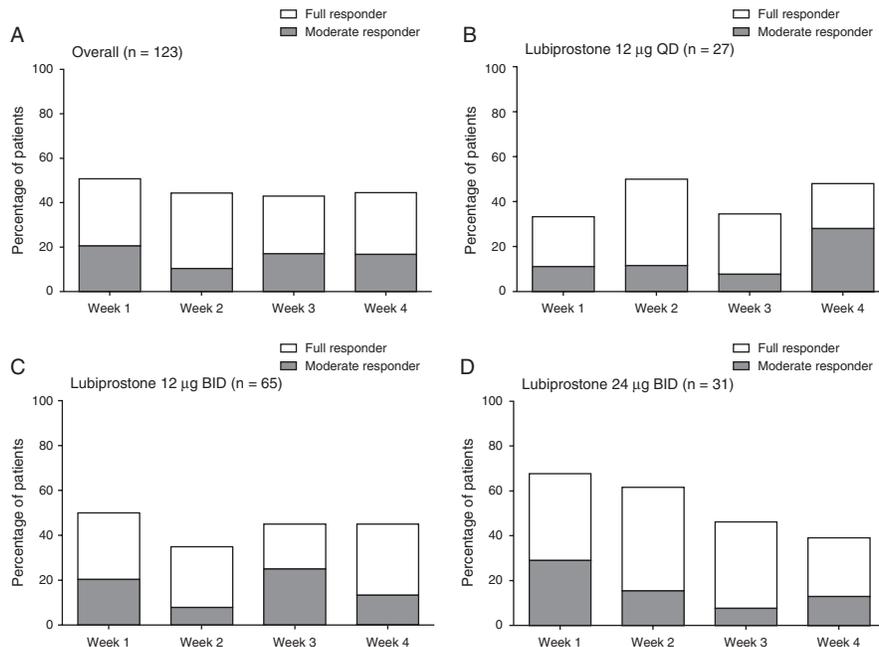


FIGURE 4. Responder rates overall (A) and in each dose group (B–D) following treatment with lubiprostone (intent-to-treat [ITT] population). Moderate responders were patients who had 3 SBMs in the given week, did not use rescue medication (including within 24 hours before that week), and did not withdraw because of lack of effectiveness; full responders had ≥4 SBMs and met the same additional criteria. BID = twice daily; ITT = intent to treat; QD = once daily; SBM = spontaneous bowel movement.

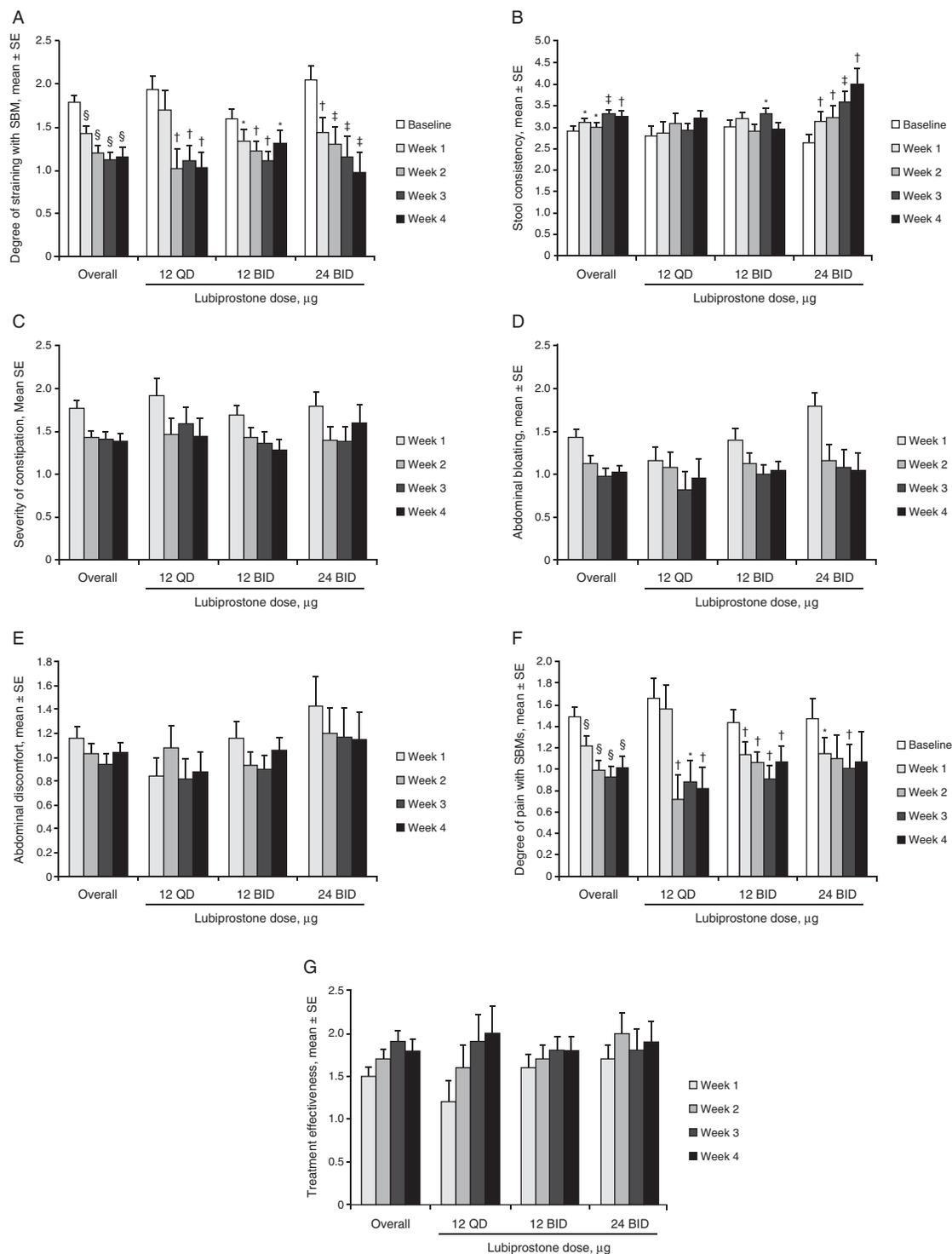


FIGURE 5. Patient ratings of constipation-associated symptoms and treatment effectiveness overall and in each dose group following treatment with lubiprostone (ITT population). Patients rated the degree of straining with SBM (A), severity of constipation (C), abdominal bloating (D), abdominal discomfort (E), and pain with SBM (F) on a 5-point scale (0 = absence of symptoms to 4 = very severe symptoms). Patients rated stool consistency (B) on the 7-point Bristol Stool Form Scale (1 = separate hard lumps like nuts to 7 = watery, no solid pieces) (21). Patients assessed treatment effectiveness (G) on a 5-point scale (0 = not at all effective to 4 = extremely effective). BID = twice daily; ITT = intent-to-treat; QD = once daily; SBM = spontaneous bowel movement. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$; § $P < 0.0001$; 1-sample t test for mean change vs baseline (A, B) or change from baseline assessed by Wilcoxon signed-rank test (F).

TABLE 2. Treatment-emergent and treatment-related adverse events (safety population)

System organ class* preferred term	Lubiprostone treatment-emergent adverse events occurring in >5% of patients in any treatment arm			Lubiprostone treatment-related adverse events in >1 patient in any treatment arm		
	12 µg QD, n = 27	12 µg BID, n = 65	24 µg BID, n = 32	12 µg QD, n = 27	12 µg BID, n = 65	24 µg BID, n = 32
At least 1 adverse event, n (%)	16 (59.3)	40 (61.5)	25 (78.1)	6 (22.2)	20 (30.8)	17 (53.1)
Gastrointestinal disorders, n (%)						
Abdominal distention	0	5 (7.7)	0	0	4 (6.2)	0
Abdominal pain	2 (7.4)	4 (6.2)	3 (9.4)	1 (3.7)	2 (3.1)	2 (6.3)
Abdominal pain, upper	1 (3.7)	3 (4.6)	2 (6.3)	0	2 (3.1)	1 (3.1)
Diarrhea	3 (11.1)	4 (6.2)	3 (9.4)	2 (7.4)	2 (3.1)	2 (6.3)
Fecaloma	0	4 (6.2)	1 (3.1)	0	0	0
Nausea	1 (3.7)	12 (18.5)	10 (31.3)	0	8 (12.3)	10 (31.3)
Vomiting	4 (14.8)	6 (9.2)	5 (15.6)	3 (11.1)	4 (6.2)	4 (12.5)
General disorders, n (%)						
Fever	4 (14.8)	1 (1.5)	0	0	0	0
Infections and infestations, n (%)						
Upper respiratory tract infection	2 (7.4)	2 (3.1)	0	0	0	0
Investigations, n (%)						
Blood cholesterol increased	2 (7.4)	1 (1.5)	1 (3.1)	0	0	0
Blood triglycerides increased	1 (3.7)	0	2 (6.3)	0	0	0
Carbon dioxide decreased	1 (3.7)	2 (3.1)	0	1 (3.7)	2 (3.1)	0
Nervous system disorders, n (%)						
Dizziness	0	1 (1.5)	3 (9.4)	0	1 (1.5)	2 (6.3)
Headache	0	4 (6.2)	3 (9.4)	0	2 (3.1)	2 (6.3)
Respiratory, thoracic, and mediastinal disorders, n (%)						
Cough	2 (7.4)	1 (1.5)	0	0	0	0

BID = twice daily; QD = once daily.

* Medical Dictionary for Regulatory Activities version 10.1.

The onset of treatment effect of lubiprostone in this study was rapid. The percentage (54.8%) of patients ≥ 36 kg achieving a first SBM within 24 hours of the first dose of lubiprostone 24 µg BID was consistent with the percentages (56.7%–61.3%) previously reported for the same dose in adults (15–17). Although onset appeared less rapid with lower doses in the present study, as previously observed in adults (17), >60% of patients had an SBM within 48 hours. These findings suggest that the onset of lubiprostone effect followed similar patterns in pediatric and adult patients.

Defecation frequency ≥ 3 /week has been widely used to define success in treating constipation in children (6). In the present study, $\geq 43\%$ of patients achieved ≥ 3 SBMs at each week without rescue medication or withdrawing from the study; however, the symptoms of pediatric constipation are partly caused by maladaptive behavior, such as contracting the pelvic floor to avoid defecation. Because the resolution of functional constipation requires a change in behavior, we anticipated that not all patients would achieve an increased frequency of SBMs when treated with lubiprostone, particularly within the 4-week duration of this study. SBM frequency was chosen as the primary endpoint for this study because reduced defecation frequency is typical of functional constipation in children (whereas withholding and fecal incontinence are not universally observed) and for consistency with previous studies in adults.

We measured subjective changes that were dependent on the mechanism of action of lubiprostone (ie, intestinal secretion of fluid) (13) and changes that were more dependent on voluntary relaxation of the pelvic floor. Patients in all treatment groups significantly improved in straining, stool consistency, and pain

with SBMs, parameters that would be expected to change with lubiprostone treatment (15–17). Treatment effects were more modest for abdominal bloating, abdominal discomfort, and constipation severity; not all patients reported these symptoms at baseline, which may have contributed to the modest mean improvements. Lubiprostone also had little effect on episodes of fecal incontinence, suggesting a potential role for maladaptive withholding behavior; however, improvements in fecal incontinence may have been restricted by the low frequency of fecal incontinence at baseline (a “floor effect”), especially in adolescent patients; thus, improvements in this outcome may have been more difficult to detect.

Lubiprostone was generally well tolerated in children and adolescents and displayed an overall safety profile similar to that observed in studies in adults, including the incidence of certain gastrointestinal AEs, such as diarrhea, abdominal pain, and abdominal distention or bloating (15–17,23). The overall incidence of nausea in this study (18.5%) was lower than in pivotal trials of the 24-µg BID dose in adults (21.0%–31.7%) (15,16). One possible explanation for this pattern in the incidence of nausea could be that pediatric patients in this study were firmly instructed to take lubiprostone with food, whereas in the previous studies in adults, instructions to take lubiprostone with food were not emphasized. The severity of nausea was rated as mild to moderate among all patients who reported this AE, and all but 1 patient experienced only single AEs of nausea. The percentage of pediatric patients in this study (7.9%) who discontinued treatment because of AEs was similar to or lower than previous studies of lubiprostone in adults with constipation (7.5% (15), 16.8% (16), 9.6% (17), and 13.3% (23)), further supporting the tolerability of lubiprostone when administered to children.

A limitation of this study was the absence of a placebo or comparator group. There is no drug presently approved for the treatment of childhood constipation that could have served as an active control in this study. A placebo-controlled study in the future would be needed to rigorously confirm efficacy in pediatric patients, given that a placebo effect on functional constipation in children treated with PEG 3350 has been demonstrated (24). Even so, the overall improvements across dose groups in SBM frequency and constipation-associated symptoms observed in this open-label study are consistent with results observed in placebo-controlled studies of lubiprostone in adults with constipation (15–17). Long-term study of lubiprostone treatment in pediatric patients has not been conducted; however, a 48-week study in adults raised no additional safety concerns compared with earlier studies of 3 to 4 weeks' duration (23). Finally, it is important to note that this study only focused on children with functional constipation; establishing the safety and effectiveness of lubiprostone in children with other conditions, such as constipation resulting from irritable bowel syndrome, would require additional studies.

CONCLUSIONS

This open-label study demonstrated the safety and effectiveness of lubiprostone when administered at doses of 12 µg QD, 12 µg BID, or 24 µg BID to children and adolescents with functional constipation. Improvements in defecation outcomes and constipation-associated symptoms were maintained across 4 weeks of observation. Treatment was generally well tolerated, and AEs were consistent with the established safety profile in adults.

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