Lubiprostone is Effective and Well Tolerated Through 48 Weeks of Treatment in Adults with Irritable Bowel Syndrome and Constipation

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Background

- Irritable bowel syndrome (IBS) is a chronic gastrointestinal (GI) disorder consisting of abdominal discomfort/pain, bloating, and altered bowel habit not explained by structural or biochemical abnormalities.
- The prevalence of IBS in Western countries is 10-15%. In the USA more than 30 million people suffer from IBS.
  - Up to 30% suffer with constipation-predominant IBS (IBS-C).
  - IBS affects more females than males, at a ratio of 2:1.
- Individuals with IBS-C experience substantial decrements in the quality of life and their ability to perform activities of daily living.
- Lubiprostone, a selective activator of type-2 chloride channels (ClC-2), is approved for the treatment of chronic idiopathic constipation in adults and for the treatment of IBS-C in adult women.
- Lubiprostone enhances fluid secretion into the intestinal lumen without altering serum electrolyte levels.
- Patients with IBS may exhibit abnormal gut permeability and an associated intestinal inflammatory response. Lubiprostone stimulates recovery of mucosal barrier function in animal models suggesting a possible mechanism for the clinical improvement observed in patients on this drug.*
- In 2 previous double-blinded placebo-controlled phase 3 trials in patients with IBS-C, lubiprostone (16 mcg) was found to be efficacious and well-tolerated for 12 weeks.

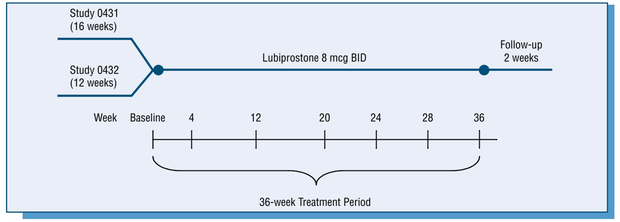
Objective

- To evaluate the long-term, efficacy, safety, and tolerability, of 16 mcg lubiprostone (8 mcg BID) when taken for up to 1 year in patients with IBS-C in an open-labeled extension of 2 randomized phase 3 trials.

Methods

- A long-term, open labeled, multicenter (130 centers in the US) phase 3 extension study of lubiprostone for the treatment of IBS-C was conducted (Figure 1).
- Patients (n=522) from 2 phase 3 double-blinded, randomized, placebo-controlled trials of lubiprostone in patients with IBS-C — SIB-0431 and SIB-0432 — entered the open-labeled extension trial for 36-weeks (Figure 2).
- Inclusion criteria
  - Patients read and signed the informed consent form.
  - Patients completed blinded treatments – 16 weeks in one study or 12 weeks in another study.
  - Patients were 70% compliant with medication in the previous studies.
- Enrollment group definitions
  - *Placebo/lubiprostone* patients took placebo in their previous trial before entering this extension study.
  - *Lubiprostone/Lubiprostone* patients took lubiprostone in their previous trial before entering the extension.
- Efficacy endpoints were obtained from each patient's evaluation of abdominal discomfort/pain, abdominal bloating, spontaneous bowel movement (SBM) frequency, stool consistency, bowel straining, constipation severity, and symptom relief.
  - Responder status was calculated from weekly assessment of symptom relief, which was assessed using a 7-point balanced scale for the following question: "How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the studies"
  - A patient was considered a monthly responder if symptoms were rated at least "moderately relieved" for all 4 weeks in a month or "significantly relieved" for at least 2 weeks within a month provided that the patient did not discontinue during the month due to lack of efficacy and there were no ratings of "moderately worse" or "significantly" worse during the month.
- Long-term safety and tolerability were monitored using standard clinical and laboratory procedures i.e. vital signs, physical examinations, weight, BMI, and laboratory test results.

Figure 1. Study Design



*Camilleri M, Gorman H. Intestinal permeability and irritable bowel syndrome. *Neurogastroenterol Motil* (2007) **19**, 545-552.

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Results

- The overall monthly responder rate for the placebo/lubiprostone and lubiprostone/lubiprostone groups increased from 19.1% and 22.3% at month 1 to 30.6% and 37.8% at month 9, respectively (Figure 3).
- Treatment with lubiprostone resulted in consistent statistically significant improvement from baseline at all months for abdominal discomfort/pain, bloating, stool consistency, straining, and constipation severity (P<0.05; Figures 4a and 4b).
- SBM Frequency did not change significantly from baseline at all months in the lubiprostone/lubiprostone group.
- No deaths were reported.
- Adverse events (AE) were reported by a total of 68.7% of patients. In 25.4% of patients AEs were considered to be treatment-related (Table 3).
- Serious adverse events (SAE) occurred in 10 patients. None of the SAEs were considered to be treatment-related.
- The most frequently reported AEs were nausea, diarrhea, abdominal distension, urinary tract infection, and sinusitis.
- No clinically meaningful trends were observed in vital signs, physical examinations, weight, BMI or laboratory test results.

Figure 2. Disposition of Patients

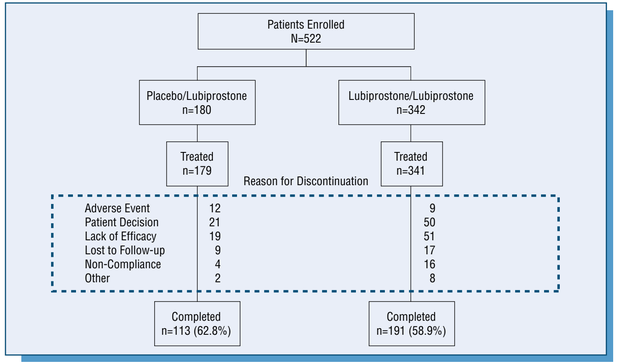


Table 1. Baseline Characteristics

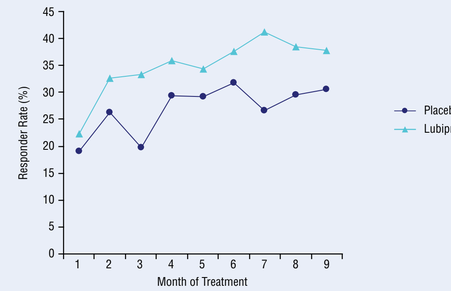
Characteristic	Enrollment Group: Placebo/Lubiprostone n=179	Enrollment Group: Lubiprostone/Lubiprostone n=341
Age (yrs)		
Mean (SD)	48.4 (12.9)	46.5 (12.0)
Range	21-82	21-81
Gender (F/M)	165/14	318/23
Race, n (%)		
Black/African American	18 (10.1)	41 (12.0)
Caucasian	146 (81.6)	269 (78.9)
Hispanic/Latino	13 (7.3)	29 (8.5)
Other	2 (1.1)	2 (0.6)

Table 2. Baseline IBS-C Symptoms

Variable	Enrollment Group: Placebo/Lubiprostone n=179 Mean (SD)	Enrollment Group: Lubiprostone/Lubiprostone n=341 Mean (SD)
Abdominal Discomfort/pain[1]	2.1 (0.6)	2.1 (0.7)
Abdominal Bloating[1]	2.3 (0.7)	2.3 (0.7)
Constipation Severity[1]	2.3 (0.7)	2.2 (0.6)
Weekly SBM Frequency	3.8 (3.4)	3.8 (3.8)
SBM Stool Consistency[2]	2.7 (0.7)	2.8 (0.7)
SBM Bowel Straining[1]	2.4 (0.7)	2.4 (0.7)

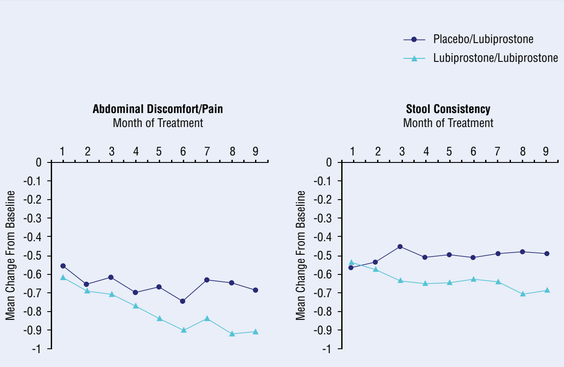
[1]Scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)
[2]Scale: 0 (Very Loose), 1 (Loose), 2 (Normal), 3 (Hard), 4 (Very Hard)

Figure 3. Monthly Responder Rates



Monthly responders were defined as patients with symptoms rated as at least "moderately relieved" for all 4 weeks within a month or "significantly relieved" for at least 2 weeks within a month.

Figure 4a. Mean Change From Baseline in IBS-C Symptoms Over Time



Significant from baseline at all months in the lubiprostone/lubiprostone group (P<0.05).

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Figure 4b. Mean Change From Baseline in IBS-C Symptoms Over Time

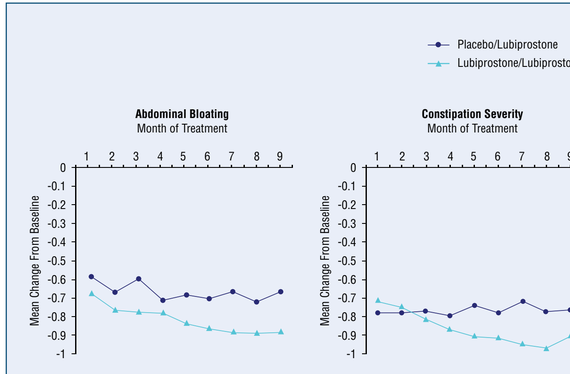

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Table 3. Summary of Adverse Events Over 36 Weeks

	Enrollment Group: Placebo/Lubiprostone n=179	Enrollment Group: Lubiprostone/Lubiprostone n=341	Enrollment Group: Overall n=520
Number (%) of patients with:			
Treatment-related adverse event	44 (24.6)	88 (25.8)	132 (25.4)
Events leading to withdrawal	14 (7.8)	12 (3.5)	26 (5.0)
At least 1 serious adverse event (SAE)	1 (0.6)	9 (2.6)	10 (1.9)
Most common AEs (>5% in any group), n (%)			
Infection and infestation	48 (26.8)	141 (41.3)	189 (36.3)
Urinary tract infection	11 (6.1)	36 (10.5)	47 (9.0)
Sinusitis	15 (8.4)	32 (9.4)	47 (9.0)
Upper respiratory track infection	5 (2.6)	20 (5.9)	25 (4.8)
Nasopharyngitis	4 (2.2)	17 (5.0)	21 (4.0)
Influenza	4 (2.2)	13 (3.8)	17 (3.3)
Gastrointestinal disorders	63 (35.2)	125 (36.7)	188 (36.2)
Nausea	17 (9.5)	40 (11.7)	57 (11.0)
Diarrhea	19 (10.6)	38 (11.1)	57 (11.0)
Abdominal distension	9 (5.0)	21 (6.2)	30 (5.8)
Abdominal pain (upper)	6 (3.4)	17 (5.0)	23 (4.4)
Nervous system disorders	14 (7.8)	47 (13.8)	61 (11.7)
Headache	7 (3.9)	19 (5.6)	26 (5.0)
Dizziness	3 (1.7)	14 (4.1)	17 (3.3)

Conclusion

- Lubiprostone at 16 mcg/day (8 mcg BID) is effective and well-tolerated for up to 1 year in patients with IBS-C.

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