Health-Related Quality of Life in Adults With Irritable Bowel Syndrome With Constipation: Results of a Combined Analysis of Two Phase 3 Studies With Lubiprostone

Douglas A. Drossman, MD[1]; William D. Chey, MD[2]; Charles Scott, PhD[3]; Raymond Panas, PhD[3]; Ryuji Ueno, MD, PhD, PhD[3]

[1]UNC Center for Functional GI and Motility Disorders, University of North Carolina, Chapel Hill, NC, USA; [2]University of Michigan Health System, Ann Arbor, MI, USA; [3]Sucampo Pharmaceuticals, Inc., Bethesda, MD, USA

Abstract

Lubiprostone is a selective activator of type-2 chloride channels approved for the treatment of chronic idiopathic constipation. Combined analyses of the quality of life (QOL) data from two Phase 3, double-blinded trials comparing lubiprostone and placebo in adults with irritable bowel syndrome and constipation (IBS-C) are presented here.

Two randomized, double-blinded, Phase 3 clinical trials compared lubiprostone (8 mcg twice daily [BID]) to placebo BID over a 12-week treatment period. All patients had IBS-C as confirmed by Rome II criteria and were at least 18 years of age. Patient-reported outcomes of IBS-C symptoms (abdominal pain/discomfort, abdominal bloating, constipation severity, straining, stool consistency, and overall symptom relief) were collected via electronic diaries prior to treatment and at Weeks 4 and 12. QOL was collected using the IBS-QOL questionnaire, which has 8 subscales: dysphoria, interference with activities, body image, health worry, food avoidance, social reaction, sexual, and relationships. A higher IBS-QOL score indicates improved QOL; a difference of 14 points is clinically meaningful.

At Week 12, change from baseline overall IBS-QOL score was higher for the lubiprostone patients compared to the placebo patients (p=0.066). There was statistically significant improvement for lubiprostone patients vs. placebo in health worry (p=0.025) and body image (p=0.015), and a trend for improvement with dysphoria (p=0.086). Lubiprostone also provided improved symptom response at Week 12 compared to placebo (also in: Drossman DA *et al*. Gastroenterology. 2007;132:2586-7[abstr]). Lubiprostone produced clinically meaningful changes (>14 points) in the IBS-QOL domains of social reaction, food avoidance, health worry, body image, and dysphoria.

Symptoms associated with IBS-C impact all aspects of QOL, with the most serious concerns being health worry and food avoidance. Lubiprostone produced clinically meaningful improvement in these important QOL domains.

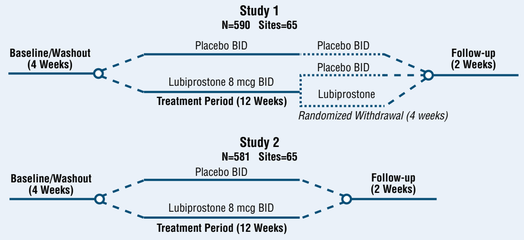
Background

- Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with an estimated prevalence of 10–15% in Western countries.
- Patients with IBS and other functional GI disorders have poorer quality of life (QOL) than the general population.
- Condition-specific QOL questionnaires have been developed to assess health-related QOL in outcome studies and clinical trials.
- Lubiprostone, a selective activator of type-2 chloride channels (CIC-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 (Camilleri, Gorman. *Neurogastroenterol Motil* 2007;19:545-552).
- In two previous double-blinded placebo-controlled Phase 3 trials in patients with IBS with constipation (IBS-C), lubiprostone (16 mcg) was found to be effective and well tolerated for 12 weeks.
- Here, we present the combined QOL data from these two Phase 3 trials which compared lubiprostone and placebo using the IBS-C QOL questionnaire (IBS-QOL), a validated disease-specific QOL measure.

Methods

- Two Phase 3, multicenter, double-blinded, randomized trials were conducted to evaluate the efficacy and safety of 16 mcg lubiprostone (8 mcg twice daily) in patients with IBS-C for 12 weeks (Figure 1).
- A total of 1164 patients were randomized in both the trials. Patients completed the IBS-QOL at randomization and weeks 4 and 12 of the treatment period.
- The IBS-QOL is a condition-specific measure of health perceptions developed for IBS. There is an overall score and 8 subscales: Dysphoria, Interference with Activities, Body Image, Health Worry, Food Avoidance, Social Reaction, Sexual, and Relationship.
- The overall and subscale scores were obtained by summing up the questions within each domain. A higher score indicated a better QOL. Prior analyses have indicated that a 14-point change in overall score is clinically meaningful (Drossman et al. *Am J Gastro* 2007;7:1442–1453).
- Differences in overall IBS-QOL and subscales by categorical factors were analyzed using analysis of variance (ANOVA) models stratified by study. To adjust for baseline differences, inferential analysis was based on changes from baseline as opposed to observed values.

Figure 1. Study Design of the Two Phase 3 Randomized Controlled Studies



Patients completed an IBS-QOL questionnaire at randomization, week 4 and week 12 of the treatment periods in both the trials.

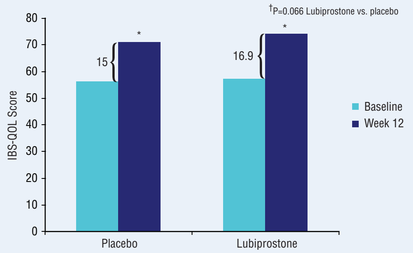
Results

- The study sample consisted primarily of middle aged Caucasian women with no differences between lubiprostone and placebo groups (Table 1).
- After 12 weeks of treatment, the change in IBS-QOL overall score trended higher in lubiprostone-treated patients compared with patients receiving placebo (16.9 vs. 15.0, P=0.066; Figure 2).
- By week 12, in both placebo- and lubiprostone-treated patients, the shift in overall IBS-QOL score from baseline was clinically meaningful (≥14 points; Figure 2).
- Treatment with lubiprostone was associated with clinically meaningful changes (≥14 points) in IBS-QOL domains of Dysphoria, Body Image, Health Worry, Food Avoidance, and Social Reaction (Figures 3a and 3b).
- Significant improvements (P<0.05) were observed in IBS-QOL domains of Health Worry and Body Image in lubiprostone-treated patients compared with patients treated with placebo (Table 2 and Figures 3a and 3b).

Table 1. Baseline Demographics

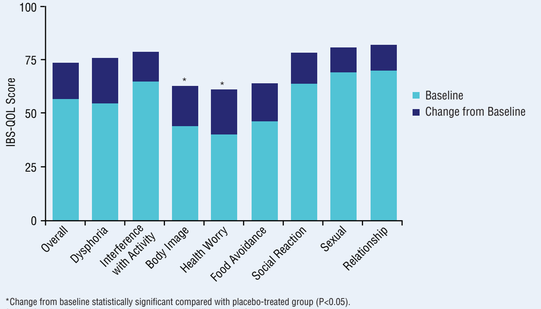
Characteristic	Treatment Group: Placebo n=385	Treatment Group: Lubiprostone n=769
Age (yrs)		
Mean (SD)	47.7 (12.9)	46.0 (12.8)
Female, %	93.3	90.8
Race, n (%)		
American Indian/Alaska Native	0 (0.0)	1 (0.1)
Asian	2 (0.5)	3 (0.4)
Black/African American	50 (13.0)	102 (13.3)
Caucasian	298 (77.4)	595 (77.4)
Hispanic/Latino	30 (7.8)	68 (8.8)
Other	5 (1.3)	0 (0.0)

Figure 2. Overall QOL



*P<0.001 at week 12 vs. baseline from a paired t-test.
†P-value is for the treatment effect from an ANOVA model controlling for the study and the baseline value.
A 14-point change in overall score is clinically meaningful.

Figure 3a. IBS-QOL Scores in Patients (n=769) Treated with Lubiprostone



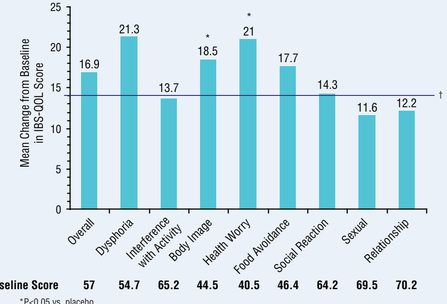
*Change from baseline statistically significant compared with placebo-treated group (P<0.05).
A 14-point change from baseline is considered clinically meaningful.

Table 2. Summary of IBS-QOL Scores

	Placebo n=385			Lubiprostone n=769		
	Baseline Mean	Week 12 Mean	Change from Baseline Mean	Baseline Mean	Week 12 Mean	Change from Baseline Mean
Overall	56.2	71.0	15.0	57.0	74.2	16.9
Subscale						
Dysphoria	53.8	72.8	19.5	54.7	76.2	21.3
Interference with Activity	64.6	76.5	11.5	65.2	78.7	13.7
Body Image	42.6	57.7	15.9	44.5	63.7	18.5*
Health Worry	40.1	57.7	17.6	40.5	62.0	21.0*
Food Avoidance	45.6	62.3	15.3	46.4	64.8	17.7
Social Reaction	63.8	75.6	12.7	64.2	78.4	14.3
Sexual	67.0	80.3	13.6	69.5	81.4	11.6
Relationship	70.3	80.9	10.9	70.2	81.8	12.2

*P<0.05 vs. placebo.
All subscales at week 12 in the placebo- and lubiprostone-treated groups were significantly changed from baseline (P<0.001).
A 14-point change from baseline is considered clinically meaningful.

Figure 3b. Change from Baseline in QOL Scores at Week 12 in Patients Treated with Lubiprostone



*P<0.05 vs. placebo.
†A 14-point change from baseline is considered clinically meaningful.

Summary and Conclusions

- Health Worry and Food Avoidance, the most serious QOL concerns in patients with IBS-C, significantly improved following treatment with lubiprostone as compared with placebo.
- Treatment with lubiprostone was also associated with clinically meaningful changes in QOL domains of Dysphoria, Food Avoidance, and Social Reaction.
- Whereas clinically meaningful changes in the overall IBS-QOL score were observed in both placebo- and lubiprostone-treated groups, the score trended higher in lubiprostone-treated patients vs. placebo-treated patients.

This study was supported by Sucampo Pharmaceuticals, Inc. and Takeda Pharmaceutical Company, Ltd.
Digestive Disease Week 2008 Scientific Meeting

E001367