Effect of Linaclotide on Severe Abdominal Symptoms in Patients With Irritable Bowel Syndrome With Constipation

Satish S. C. Rao,[*] Eamonn M. M. Quigley,[‡] Steven J. Shiff,[§] Bernard J. Lavins,[‖] Caroline B. Kurtz,[‖] James E. MacDougall,[‖] Mark G. Currie,[‖] and Jeffrey M. Johnston[‖]

*Section of Gastroenterology and Hepatology, Georgia Regents University, Augusta, Georgia; [‡]Gastroenterology Division, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Texas; [§]Forest Research Institute, Jersey City, New Jersey; and [‖]Ironwood Pharmaceuticals, Cambridge, Massachusetts

BACKGROUND & AIMS: **Patients with irritable bowel syndrome with constipation (IBS-C) have abdominal symptoms that vary in severity. Linaclotide, a guanylate cyclase-C agonist, improves abdominal and bowel symptoms in these patients. We examined the prevalence of severe abdominal symptoms in patients with IBS-C and assessed the effects of linaclotide on abdominal symptoms, global measures, and quality of life (QOL).**

METHODS: **In two phase 3 trials, patients who met modified Rome II criteria for IBS-C were randomly assigned to groups given oral, once-daily linaclotide (290 μg) or placebo for 12 weeks. During the baseline (2 weeks prior to treatment) and treatment periods, patients rated abdominal pain, discomfort, bloating, fullness, and cramping daily (from 0 = none to 10 = very severe). Linaclotide's effects on abdominal symptoms, global measures, and IBS-related QOL were assessed in subpopulations of patients who rated specific individual abdominal symptoms as severe (≥7.0) at baseline.**

RESULTS: **In the intent-to-treat population (1602 patients; 797 receiving placebo and 805 receiving linaclotide), baseline prevalence values for severe abdominal symptoms were 44% for bloating, 44% for fullness, 32% for discomfort, 23% for pain, and 22% for cramping, with considerable overlap among symptoms. In patients with severe symptoms, linaclotide reduced all abdominal symptoms; mean changes from baseline severity scores ranged from −2.7 to −3.4 for linaclotide vs −1.4 to −1.9 for placebo ($P < .0001$). Linaclotide improved global measures ($P < .0001$) and IBS-QOL scores ($P < .01$) compared with placebo. Diarrhea was the most common adverse event of linaclotide in patients with severe abdominal symptoms (18.8%–21.0%).**

CONCLUSIONS: **Of 5 severe abdominal symptoms assessed, bloating and fullness were most prevalent in patients with IBS-C. Linaclotide significantly improved all abdominal symptoms, global measures, and IBS-QOL in subpopulations of IBS-C patients with severe abdominal symptoms. Clinicaltrials.gov Numbers: NCT00938717, NCT00948818.**

Keywords: Guanylate Cyclase-C; IBS-C; Abdominal Pain; Bloating.

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder affecting up to 15% of the population in developed countries.[1–3] IBS is characterized by abdominal pain or discomfort associated with altered defecation[4] and is classified on the basis of predominant stool form into 4 subtypes: IBS with diarrhea, IBS with constipation (IBS-C), mixed IBS, and unsubtyped IBS.[4]

Patients with IBS-C often experience an array of abdominal symptoms, including pain, discomfort, bloating, fullness, and cramping, that vary in severity. The severity of abdominal symptoms has significant clinical implications because patients with more severe symptoms tend to use more health care resources, have worse health-related quality of life (QOL), and be less likely to respond to treatment.[5,6] Symptom severity is also an important component of a patient's perception of his/her overall IBS severity.[5] Despite the importance of symptom

Abbreviations used in this paper: **AE, adverse event; ANCOVA, analysis of covariance; BM, bowel movement; cGMP, cyclic guanosine monophosphate; CMH, Cochran–Mantel-Haenszel; GC-C, guanylate cyclase-C; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; ITT, intent to treat; IVRS, interactive voice response system; LOCF, last observation carried forward; NNT, number needed to treat; NRS, numerical rating scale; QOL, quality of life.**

1542-3565
http://dx.doi.org/10.1016/j.cgh.2013.09.022

severity, there are scant data regarding the prevalence of symptoms that IBS-C patients rate as severe.

Linaclotide, a 14-amino acid peptide, is a guanylate cyclase-C (GC-C) agonist that is structurally related to the guanylin peptide family and is approved by the United States Food and Drug Administration for the treatment of IBS-C and chronic idiopathic constipation in adults and by the European Medicines Agency for the treatment of moderate to severe IBS-C in adults. Linaclotide binds to and activates GC-C, resulting in the intracellular generation of cyclic guanosine monophosphate (cGMP), which is then increased both intracellularly and extracellularly. Data from animal models show that the increase in intracellular cGMP results in a cascade of events leading to increased fluid secretion into the intestinal lumen and accelerated gastrointestinal transit; the increase in extracellular cGMP results in reduced visceral nociception.[7,8]

In two phase 3 clinical trials, linaclotide has been shown to improve abdominal and bowel symptoms in patients with IBS-C.[9,10] However, the efficacy of linaclotide in IBS-C patients with severe symptoms has not been examined. To address this issue, a post hoc analysis of pooled data from the two phase 3 trials was conducted with the following objectives: (1) to examine the baseline prevalence of severe abdominal symptoms (pain, discomfort, bloating, fullness, cramping) and (2) to assess the effects of linaclotide on these symptoms, as well as on global measures of improvement (adequate relief, degree of relief, and treatment satisfaction) and IBS-related QOL, in the subpopulations of IBS-C patients with severe abdominal symptoms at baseline.

Methods

Trial Design

Detailed study methods for both phase 3 clinical trials (Trials 31 and 302) have been recently published.[9,10] In brief, these multicenter, randomized, double-blind, placebo-controlled, parallel-group trials were identical through the first 12 weeks of treatment. The trials included a 2-week baseline period that was followed by randomization of patients in equal proportions to either placebo or linaclotide 290 μg once daily during treatment periods of either 12 weeks (Trial 31) or 26 weeks (Trial 302). Primary end points were assessed for both trials during the first 12 weeks of treatment.

Trial Patients

Inclusion and exclusion criteria for the trials have been published previously.[9,10] Briefly, female and male patients were eligible to participate if they were at least 18 years of age and met modified Rome II criteria for IBS-C.[11] Patients had to have a mean score $\geq$3.0 for daily abdominal pain at its worst (11-point numerical rating scale [NRS]) as well as a mean of $\leq$5 spontaneous bowel movements (a bowel movement [BM] occurring in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM) per week and $<$3 complete spontaneous BMs (a spontaneous BM that is associated with a sensation of complete emptying) per week during the 2-week baseline period.

Efficacy Assessments and Severe Subpopulation Criterion

Daily reports by patients to an interactive voice response system (IVRS) included symptom ratings of abdominal pain at its worst, abdominal discomfort, abdominal bloating, abdominal fullness, and abdominal cramping. All abdominal symptoms were measured by using the 11-point NRS (example question: "How would you rate your abdominal discomfort over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal discomfort and 10 represents very severe abdominal discomfort."). The severe subpopulation for each abdominal symptom included patients in the intent-to-treat (ITT) population with a baseline score $\geq$7.0[12] for that abdominal symptom. Patients were included in more than 1 subpopulation if they had more than 1 abdominal symptom scored $\geq$7.0 at baseline.

Weekly IVRS assessments of global measures of improvement included adequate relief of IBS-C symptoms (yes/no) and degree of relief of IBS symptoms (7-point balanced scale: 1 = completely relieved, 4 = unchanged, 7 = as bad as I can imagine). Satisfaction with the trial medication's ability to relieve IBS symptoms (5-point ordinal scale: 1 = not at all satisfied to 5 = very satisfied) was assessed at all trial visits. The IBS-QOL, a self-administered QOL instrument yielding an overall score ranging from 0 (poor QOL) to 100 (maximum QOL),[13] was assessed at baseline and at week 12.

End Points

Change-from-baseline end points for abdominal symptoms (pain, discomfort, bloating, fullness, and cramping) were analyzed at week 12. Responder end points for adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, treatment satisfaction, and IBS-QOL overall score were also analyzed at week 12; the number needed to treat (NNT) was calculated for each of these end points. Adequate relief responders answered "yes" to the question "Overall, have you had adequate relief from your IBS symptoms during the past 7 days?" Degree of relief responders had a degree of relief of IBS symptoms score of $\leq$3 (somewhat relieved, considerably relieved, or completely relieved) on the 7-point balanced scale. Treatment satisfaction responders had a treatment satisfaction score of $\geq$3 (moderately, quite, or very satisfied) on the 5-point scale. IBS-QOL responders had a change-from-baseline improvement of $\geq$14 points on the

IBS-QOL overall score; this level of improvement was determined to be clinically meaningful on the basis of previous research by Drossman et al.[14] For all end points analyzed, if a patient discontinued from the trial or had missing data at week 12, a last-observation-carried-forward (LOCF) method was applied; patients with no post-baseline assessments of the end point were excluded from the analysis.

Safety Assessments

At each study visit, patients were asked an open-ended question regarding adverse events (AEs). Patients reported AEs by recalling instances since their prior visit. The site investigator recorded all patient-reported AEs and judged each event for severity and relationship to the blinded trial medication. Other safety evaluations included physical examinations, electrocardiogram recordings, vital sign measurements, and standard clinical laboratory tests.

Statistical Methods

All analyses were based on pooled results from the two phase 3 trials. The safety population included patients who received ≥1 dose of double-blind trial medication during the treatment period. The ITT population included patients in the safety population who had ≥1 post-randomization assessment of abdominal pain or BM frequency.[9,10]

End points were evaluated in each severe abdominal symptom subpopulation (baseline severity scores ≥7 on the 11-point NRS; hereafter, severe subpopulation) and in the ITT population. Continuous change-from-baseline end points were analyzed by using an analysis of covariance (ANCOVA) model with treatment group, geographic region, and study as factors and the corresponding baseline value as a covariate. The change-from-baseline means are least-squares means from the corresponding ANCOVA model. Responder end points were analyzed by using a Cochran–Mantel-Haenszel (CMH) test controlling for study and geographic region.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Analysis Populations and Demographics

The pooled ITT population comprised 1602 patients (Table 1). The abdominal symptoms with the highest prevalence of mean baseline severity scores ≥7.0 were fullness and bloating (44% for both, Figure 1), followed by discomfort (32%), pain (23%), and cramping (22%). Because IBS-C patients generally experience multiple abdominal symptoms, it is not surprising that there was considerable overlap in these 5 severe subpopulations. In particular, 90% of the patients in the bloating subpopulation were also in the fullness subpopulation and vice versa (Figure 2*A*). Similarly, more than 80% of those who reported severe pain also reported severe cramping and vice versa (Figure 2*B*). The overlap was somewhat less for other symptom pairings. Because of these overlaps, efficacy results will only be reported for 3 representative subpopulations, the pain, discomfort, and

Table 1. Demographic and Baseline Clinical Characteristics

	Severe abdominal symptom subpopulations				
	Severe pain (n = 376)	Severe discomfort (n = 507)	Severe bloating (n = 702)	All 3 symptoms severe (n = 339)	ITT population (N = 1602)
Demographic data					
Age (*y*), mean (range)	43.2 (19–81)	43.2 (18–81)	43.4 (18–81)	43.6 (19–81)	43.9 (18–87)
≥65, n (%)	12 (3.2)	15 (3.0)	22 (3.1)	12 (3.5)	85 (5.3)
Sex, n (%)					
Female	343 (91.2)	468 (92.3)	666 (94.9)	314 (92.6)	1443 (90.1)
Male	33 (8.8)	39 (7.7)	36 (5.1)	25 (7.4)	159 (9.9)
Race, n (%)					
White	285 (75.8)	390 (76.9)	531 (75.6)	254 (74.9)	1240 (77.4)
Black	71 (18.9)	95 (18.7)	147 (20.9)	66 (19.5)	301 (18.8)
Other	20 (5.3)	22 (4.3)	24 (3.4)	19 (5.6)	61 (3.8)
Abdominal symptoms,[a] mean					
Abdominal pain	8.0	7.5	6.8	8.1	5.6
Abdominal discomfort	8.2	8.0	7.4	8.3	6.1
Abdominal bloating	8.4	8.4	8.3	8.6	6.6
Abdominal fullness	8.4	8.4	8.2	8.5	6.6
Abdominal cramping	7.7	7.2	6.5	7.7	5.3
IBS-QOL overall[b]	51.3	52.2	55.5	50.4	61.1

[a]Assessed by using 11-point NRS: 0 = none, 10 = very severe.
[b]Score ranging from 0 (poor QOL) to 100 (maximum QOL).

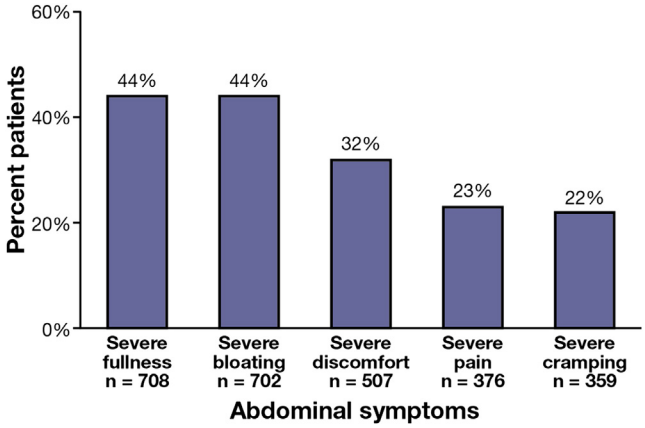

Figure 1. Percentages of patients with mean baseline abdominal symptom score ≥7.0. For each symptom, the percentage of patients with a mean baseline score ≥7.0 is presented. The denominator is the pooled ITT population (N = 1602).

bloating subpopulations, as well as for a fourth subpopulation of ITT patients with baseline scores ≥7.0 for all 3 of these abdominal symptoms (pain, discomfort, and bloating; Figure 2*C*). Demographic characteristics were similar between each of these 4 subpopulations and the pooled ITT population, although the subpopulations tended to be younger, more female, and more non-white than the ITT population. Not surprisingly, the baseline QOL as measured by the IBS-QOL was worse in the severe subpopulations compared with the ITT population (50 to 56 vs 61 on a 100-point scale; Table 1).

Efficacy Results

In each of the 4 severe subpopulations, the mean changes from baseline for abdominal pain, discomfort, bloating, fullness, and cramping were significantly greater for linaclotide-treated patients at week 12 compared with placebo-treated patients (Table 2, $P < .0001$). In addition, for each of these symptoms, the mean changes for linaclotide-treated patients were higher in the severe subpopulations than in the ITT population. Moreover, for each of these symptoms, the corresponding differences between linaclotide-treated and placebo-treated patients (ie, the treatment effects) were higher in the severe subpopulations than in the ITT population (Table 2).

For all 3 global responder end points, linaclotide-treated patients in the severe subpopulations had significantly better response rates than placebo-treated patients. Across the severe subpopulations, 59%–61% of linaclotide-treated patients reported adequate relief of IBS symptoms at week 12 compared with 28%–32% of placebo-treated patients (Figure 3*A*, $P < .0001$ for linaclotide vs placebo in all severe subpopulations); NNTs ranged from 3.0–3.7. For degree of relief of IBS symptoms, 73%–75% of linaclotide-treated patients reported that their symptoms were somewhat, considerably, or completely relieved at week 12 compared with 43%–47% of placebo-treated patients (Figure 3*B*, $P < .0001$ for linaclotide vs placebo in all severe subpopulations); NNTs ranged from 3.2–3.8. Likewise, 70%–77% of linaclotide-treated patients reported being moderately, quite, or very satisfied with treatment at week 12 compared with 41%–43% of placebo-treated patients (Figure 3*C*, $P < .0001$ for linaclotide vs placebo in all severe subpopulations); NNTs ranged from 2.9–3.6. For the IBS-QOL analysis, 62%–68% of linaclotide-treated patients were IBS-QOL responders, compared with 45%–47% of placebo patients (Figure 3*D*, $P < .01$ for linaclotide vs placebo in all severe subpopulations); NNTs ranged from 4.7–6.0.

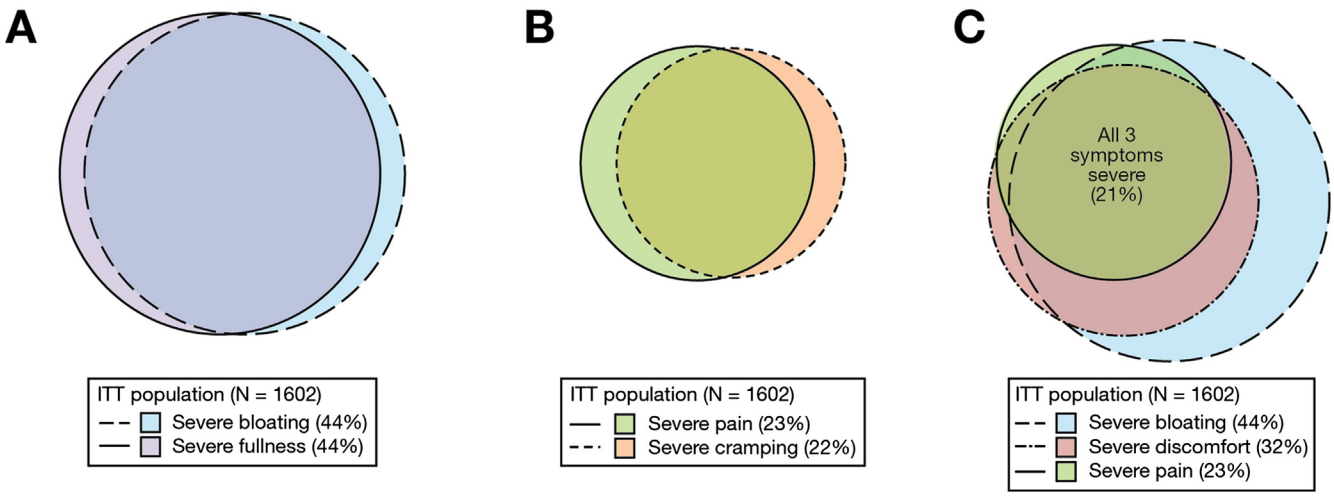

Figure 2. Severe abdominal symptom subpopulations (mean baseline severity score ≥7.0). (*A*) The severe bloating and severe fullness subpopulations each represent 44% of the ITT population and overlap each other by 90%. (*B*) The severe pain and severe cramping subpopulations represent 23% and 22% of the ITT population, respectively, and overlap each other by more than 80%. (*C*) The severe bloating, severe discomfort, and severe pain subpopulations represent 44%, 32%, and 23% of the ITT population, respectively, and were chosen for analyses. The intersection of these 3 subpopulations represents the all 3 symptoms severe subpopulation that includes patients with mean baseline scores ≥7.0 for abdominal pain, abdominal discomfort, and abdominal bloating (21% of the ITT population).

Table 2. Week 12 Change From Baseline in Abdominal Symptoms

Abdominal symptoms[a]	Severe abdominal symptom subpopulations				ITT population (N = 1602)
	Severe pain (n = 376)	Severe discomfort (n = 507)	Severe bloating (n = 702)	All 3 symptoms severe (n = 339)	
Pain					
PBO mean (SE)	−1.87 (0.22)	−1.64 (0.19)	−1.43 (0.16)	−1.74 (0.24)	−1.31 (0.09)
LIN mean (SE)	−3.34 (0.21)	−3.13 (0.18)	−2.74 (0.15)	−3.42 (0.23)	−2.21 (0.09)
Difference	−1.48	−1.49	−1.31	−1.68	−0.91
P value	<.0001	<.0001	<.0001	<.0001	<.0001
Discomfort					
PBO mean (SE)	−1.81 (0.22)	−1.77 (0.19)	−1.59 (0.16)	−1.69 (0.24)	−1.38 (0.09)
LIN mean (SE)	−3.27 (0.21)	−3.28 (0.18)	−2.89 (0.15)	−3.37 (0.22)	−2.30 (0.09)
Difference	−1.46	−1.51	−1.29	−1.68	−0.93
P value	<.0001	<.0001	<.0001	<.0001	<.0001
Bloating					
PBO mean (SE)	−1.56 (0.22)	−1.57 (0.19)	−1.61 (0.16)	−1.49 (0.24)	−1.29 (0.09)
LIN mean (SE)	−3.11 (0.22)	−3.10 (0.18)	−2.90 (0.15)	−3.23 (0.23)	−2.26 (0.09)
Difference	−1.54	−1.54	−1.29	−1.73	−0.98
P value	<.0001	<.0001	<.0001	<.0001	<.0001
Fullness					
PBO mean (SE)	−1.55 (0.22)	−1.54 (0.19)	−1.52 (0.16)	−1.46 (0.24)	−1.33 (0.09)
LIN mean (SE)	−3.12 (0.22)	−3.14 (0.18)	−2.92 (0.15)	−3.22 (0.23)	−2.35 (0.09)
Difference	−1.57	−1.61	−1.40	−1.77	−1.02
P value	<.0001	<.0001	<.0001	<.0001	<.0001
Cramping					
PBO mean (SE)	−1.79 (0.22)	−1.67 (0.18)	−1.50 (0.15)	−1.72 (0.24)	−1.32 (0.09)
LIN mean (SE)	−3.18 (0.21)	−3.04 (0.17)	−2.66 (0.14)	−3.27 (0.23)	−2.12 (0.08)
Difference	−1.38	−1.38	−1.16	−1.55	−0.80
P value	<.0001	<.0001	<.0001	<.0001	<.0001

NOTE. Week 12 (LOCF) change-from-baseline least-squares means presented; *P* value for all analyses based on a comparison of linaclotide vs placebo in ANCOVA model with treatment group, geographic region, and study as factors and baseline value as covariate.
LIN, linaclotide; PBO, placebo; SE, standard error.
[a]Assessed by using 11-point NRS: 0 = none, 10 = very severe.

Safety Results

Approximately 50% of both linaclotide-treated and placebo-treated patients in all the severe subpopulations experienced at least 1 AE (Table 3). As in the safety population, diarrhea was the most common AE in the severe subpopulations, occurring in 18.3%–19.8% of linaclotide-treated patients and in 1.6%–2.1% of placebo-treated patients. Similar to rates observed in the safety population, flatulence occurred at higher rates in linaclotide-treated (4.2%–5.7%) vs placebo-treated (1.8%–2.5%) patients in the severe subpopulations. The rate of abdominal pain AEs for linaclotide-treated patients in the severe subpopulations ranged from 2.1%–4.0% compared with 2.2%–2.5% for placebo-treated patients and was lower compared with linaclotide-treated patients in the safety population (5.1%).

Discussion

These findings provide a new understanding of the nature of illness in patients with IBS-C. The overall severity of IBS comprises multiple elements, including physical symptoms as well as health-related QOL, psychosocial factors, health-care utilization behaviors, and burden of illness.[5] Of the abdominal symptoms experienced by patients, pain or discomfort is considered a clinical hallmark of IBS and, as such, baseline abdominal pain was an entry criterion for the two linaclotide phase 3 clinical trials. Although this trial population was selected for pain (mean baseline abdominal pain score $\geq$3.0), a higher proportion of patients rated abdominal bloating and fullness as severe (44% each) than rated discomfort, pain, or cramping as severe (32%, 23%, and 22%, respectively) at baseline. This symptom pattern suggests that the presence of bloating and fullness in patients with IBS-C may warrant greater attention in clinical practice as well as in clinical trial design. Indeed, previous analyses have shown that abdominal pain and bloating are both significant predictors of overall IBS severity[15] and are both among the most frequently reported factors contributing to patient perception of IBS severity.[6] The proportions of patients in this analysis with abdominal symptoms rated as severe, 22%–44%, are consistent with international survey data in which 35% of IBS patients reported their symptoms as severe.[6] Many patients in this analysis rated more than 1 abdominal symptom as severe, as evidenced by the considerable overlap among the severe subpopulations. The multisymptom aspect of IBS in

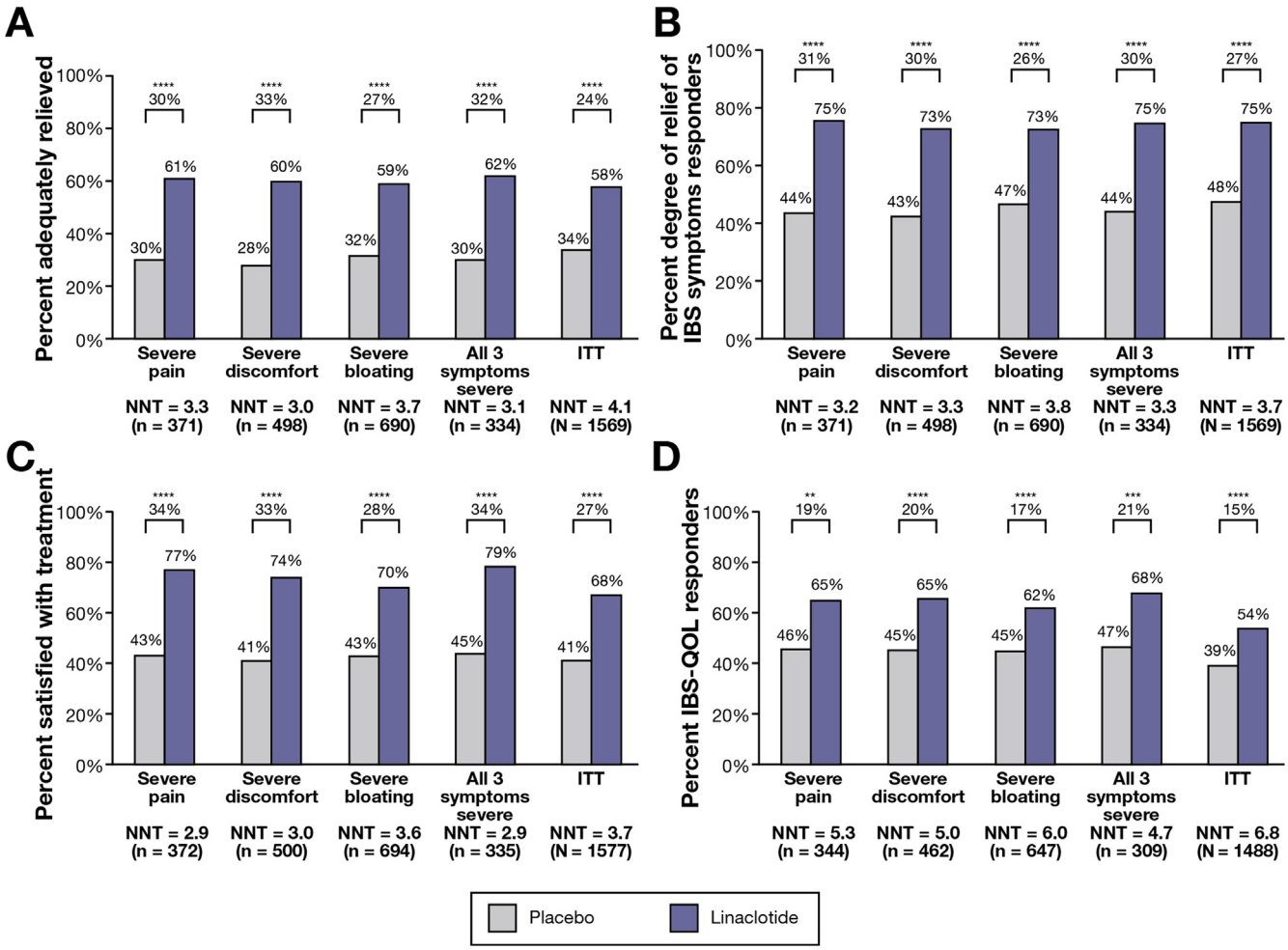

Figure 3. Effect of linaclotide on global measures and IBS-QOL overall score in severe abdominal symptom subpopulations at week 12. (*A*) Adequate relief in patients with abdominal symptom scores ≥7.0 at baseline (week 12 LOCF). ****$P < .0001$ for linaclotide vs placebo by using a CMH test. Note: scale for adequate relief responders: yes, no (dichotomous scale). (*B*) Degree of relief of IBS symptoms in patients with abdominal symptom scores ≥7.0 at baseline (week 12 LOCF). ****$P < .0001$ for linaclotide vs placebo by using a CMH test. Note: scale for degree of relief of IBS symptoms: completely relieved, considerably relieved, somewhat relieved, unchanged, somewhat worse, considerably worse, or as bad as I can imagine. Responders had a degree of relief of IBS symptoms that was somewhat relieved, considerably relieved, or completely relieved (ie, ≤3 on the 7-point balanced scale). (*C*) Treatment satisfaction in patients with abdominal symptom scores ≥7.0 at baseline (week 12 LOCF). ****$P < .0001$ for linaclotide vs placebo by using a CMH test. Note: scale for treatment satisfaction: not at all satisfied, somewhat satisfied, moderately satisfied, quite satisfied, or very satisfied. Percent satisfied = % of patients who were moderately, quite, or very satisfied (ie, ≥3 on the 5-point ordinal scale). (*D*) IBS-QOL improvement in patients with abdominal symptom scores ≥7.0 at baseline. Responders had a change from baseline to week 12 (LOCF) in IBS-QOL overall score of ≥14 points (on a 0–100 scale). **$P < .01$, ***$P < .001$, ****$P < .0001$ for linaclotide vs placebo by using a CMH test.

patients in this analysis supports the concept of IBS as a complex disease characterized by a combination of symptoms[6] that vary over time and in severity.[16]

In IBS-C patients with 1 or more severe abdominal symptoms, linaclotide significantly improved abdominal pain, discomfort, bloating, fullness, and cramping. In fact, in the severe subpopulations, linaclotide treatment resulted in greater symptom improvement from baseline than in the ITT population, which also included patients with milder baseline symptoms. Moreover, linaclotide treatment resulted in greater differences from placebo in the severe subpopulations than in the ITT population. Thus, whereas the phase 3 clinical trials demonstrated that linaclotide is effective in the treatment of symptoms in IBS-C patients,[9,10] the current post hoc analyses further demonstrate that linaclotide is effective in the treatment of IBS-C patients with severe abdominal symptoms.

In addition, significantly more linaclotide-treated patients than placebo-treated patients were IBS-QOL responders, indicating that in patients with severe abdominal symptoms at baseline, linaclotide is effective in improving IBS-related QOL in a clinically meaningful way. Linaclotide also significantly improved the 3 global measures (adequate relief of IBS symptoms, degree of relief of IBS symptoms, and treatment satisfaction) in the severe subpopulations.

For IBS-QOL and the 3 global measures, the differences from placebo for the severe pain and severe discomfort

Table 3. Adverse Events

	Severe abdominal symptom subpopulations									
	Severe pain		Severe discomfort		Severe bloating		All 3 symptoms severe		Safety population	
	PBO (n = 185)	LIN (n = 192)	PBO (n = 242)	LIN (n = 266)	PBO (n = 324)	LIN (n = 379)	PBO (n = 164)	LIN (n = 176)	PBO (n = 798)	LIN (n = 807)
Patients with at least 1 AE, n (%)	96 (51.9)	101 (52.6)	126 (52.1)	139 (52.3)	170 (52.5)	204 (53.8)	85 (51.8)	91 (51.7)	438 (54.9)	491 (60.8)
Diarrhea, n (%)	3 (1.6)	38 (19.8)	5 (2.1)	50 (18.8)	6 (1.9)	72 (19.0)	3 (1.8)	37 (21.0)	24 (3.0)	160 (19.8)
Abdominal pain, n (%)	4 (2.2)	4 (2.1)	6 (2.5)	6 (2.3)	8 (2.5)	15 (4.0)	4 (2.4)	2 (1.1)	26 (3.3)	41 (5.1)
Flatulence, n (%)	4 (2.2)	11 (5.7)	6 (2.5)	12 (4.5)	6 (1.9)	18 (4.7)	4 (2.4)	10 (5.7)	15 (1.9)	35 (4.3)

NOTE. AEs reported in ≥5% of linaclotide-treated patients and at incidence greater than reported in placebo-treated patients during the treatment period.
LIN, linaclotide; PBO, placebo.

subpopulations were greater than the differences from placebo for the severe bloating subpopulation, which more closely resembled those of the ITT population. This finding may reflect the baseline symptom profiles of these subpopulations. In the severe pain and severe discomfort subpopulations, mean baseline scores were severe (≥7.0) not just for the eponymous symptoms but for all 5 abdominal symptoms (pain, discomfort, bloating, fullness, and cramping), whereas in the severe bloating population, mean baseline scores were severe for bloating, fullness, and discomfort but not for pain (6.8) and cramping (6.5).

The rate of AEs was similar between linaclotide and placebo groups in each of the severe subpopulations (approximately 50%). This rate was slightly lower than the AE rate observed for the overall safety population, in which AEs were reported by 60.8% and 54.9% of linaclotide and placebo patients, respectively. Similar to the overall safety population data, the most common AE in the severe subgroups was diarrhea, which was reported by 18.8%–21.0% of linaclotide-treated patients and by 1.6%–2.1% of placebo-treated patients.

The treatment of patients with severe symptoms of IBS is challenging and is often aimed at managing individual symptoms.[16] Linaclotide not only improves severe abdominal and bowel symptoms but also improves patient-perceived global relief of IBS symptoms and QOL in these patients with severe abdominal symptoms. Thus, linaclotide offers an effective treatment for the overall management of IBS-C patients with severe abdominal symptoms.

There are several important caveats to this analysis. First, patients in these clinical trials did not rate how bothersome their symptoms were. Therefore, it cannot be determined how the numerical rating of symptom severity may correlate with how bothersome a symptom is to a patient. For example, a patient may have rated abdominal bloating = 8 and abdominal pain = 6, but it is possible that abdominal pain may have been more bothersome to that patient than abdominal bloating. Second, the trial population may not be representative of all IBS-C patients because entry into these trials required patients to have a mean baseline abdominal pain score of ≥3.0 in addition to meeting other inclusion and exclusion criteria.[17]

In summary, this analysis demonstrated that abdominal bloating and fullness are key components of the spectrum of illness in IBS-C, particularly in patients reporting more severe symptoms. Those patients with severe abdominal symptoms responded to linaclotide treatment just as well as, if not better than, the ITT population, which included patients with milder abdominal symptoms. Thus, linaclotide can be effective in the management of IBS-C patients with severe abdominal symptoms, including abdominal bloating and fullness. Furthermore, linaclotide-treated patients in the severe subpopulations experienced meaningful improvements in global measures and IBS-related QOL.

References

1. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based systematic review on the management of irritable bowel syndrome. Am J Gastroenterol 2009;104:1–40.
2. Hungin AP, Chang L, Locke GR, et al. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005;21:1365–1375.
3. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–650.
4. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006;130:1480–1491.
5. Lembo A, Ameen VZ, Drossman DA. Irritable bowel syndrome: toward an understanding of severity. Clin Gastroenterol Hepatol 2005;3:717–725.
6. Drossman DA, Morris CB, Schneck S, et al. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J Clin Gastroenterol 2009;43:541–550.
7. Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. Neurogastroenterol Motil 2010;22:312–322.
8. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci 2010;8:19–20.

9. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107:1714–1725.
10. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012;107:1702–1712.
11. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gut 1999; 45(Suppl 2):II43–II47.
12. McCaffery M, Beebe A. Pain: clinical manual for nursing practice . Balitimore, MD: V.V. Mosby Company, 1993.
13. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci 1998;43:400–411.
14. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol 2000;95:999–1007.
15. Spiegel B, Strickland A, Naliboff BD, et al. Predictors of patient-assessed illness severity in irritable bowel syndrome. Am J Gastroenterol 2008;103:2536–2543.
16. Mayer EA. Clinical practice: irritable bowel syndrome. N Engl J Med 2008;358:1692–1699.
17. Videlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. Clin Gastroenterol Hepatol 2013; 11:1084–1092.

Reprint requests
Address requests for reprints to: Jeffrey M. Johnston, MD, Ironwood Pharmaceuticals, Inc, 301 Binney Street, Cambridge, Massachusetts 02142. e-mail: jjohnston@ironwoodpharma.com; fax: (617) 494-0480.

Conflicts of interest
The authors disclose the following: Jeffrey Johnston, Caroline Kurtz, James MacDougall, Bernard Lavins, and Mark Currie are employees of Ironwood Pharmaceuticals and own stock/stock options in Ironwood Pharmaceuticals. Steven Shiff is an employee of Forest Laboratories and owns stock/stock options in Forest Laboratories. Satish S. C. Rao participated as a principal investigator and has served on the advisory boards and received honoraria from Ironwood Pharmaceuticals and Forest Research Institute. Eamonn M. M. Quigley has served on the advisory boards for Ironwood Pharmaceuticals and Forest Research Institute.

Funding
Supported by Forest Research Institute and Ironwood Pharmaceuticals, Inc.