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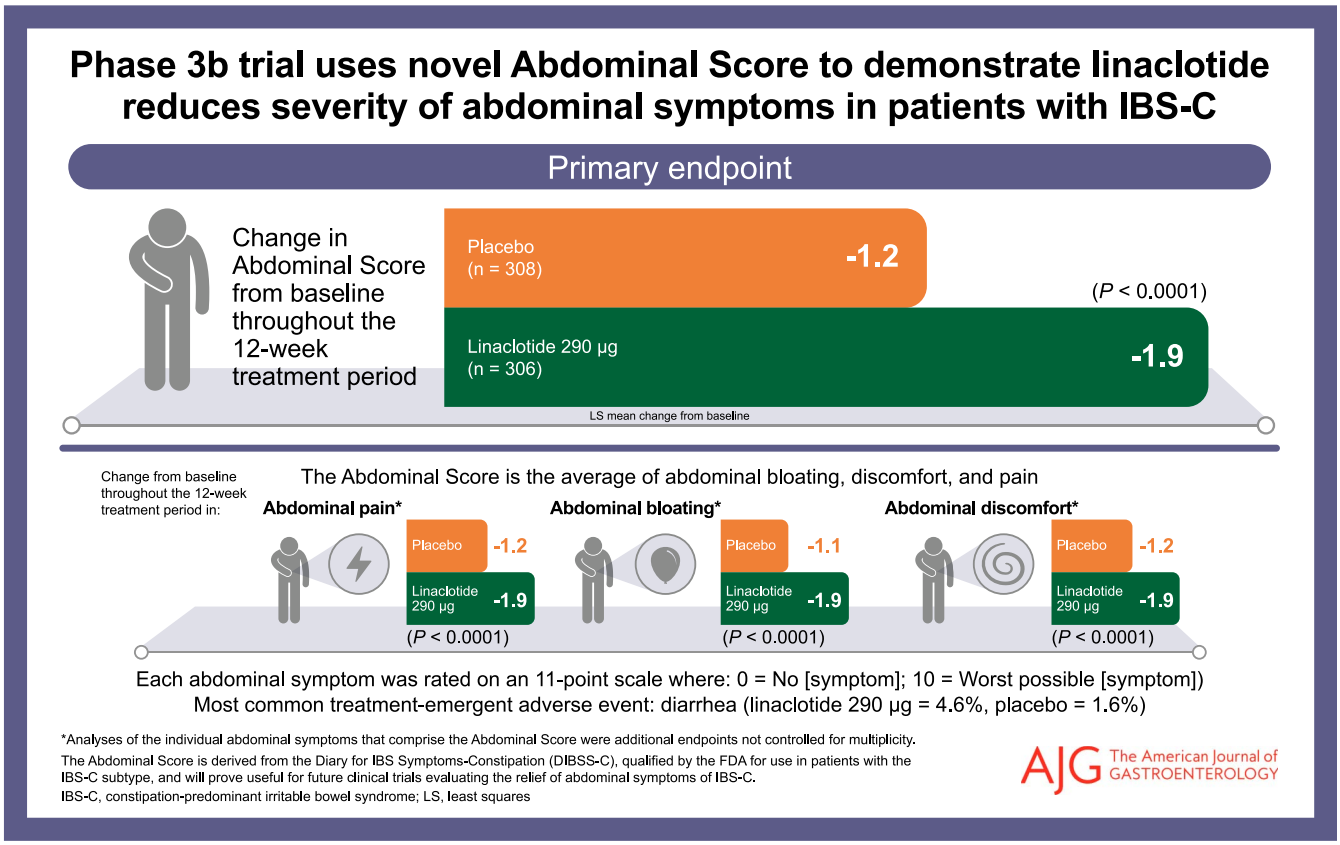
Efficacy of Linaclotide in Reducing Abdominal Symptoms of Bloating, Discomfort, and Pain: A Phase 3B Trial Using a Novel Abdominal Scoring System

Lin Chang, MD[1], Brian E. Lacy, MD, PhD[2], Baha Moshiree, MD, MSc[3], Amy Kassebaum, PA-C, MMS, RD[4], Jessica L. Abel, MPH[5], Jennifer Hanlon, MPH[6], Wilmin Bartolini, PhD[7], Ramesh Boinpally, PhD[5], Wieslaw Bochenek, MD[8], Susan M. Fox, PhD[5], Madhuja Mallick, PhD[5], Ken Tripp, PhD[6,9], Nicholas Omniewski, MPH[7], Elizabeth Shea, PhD[7] and Niels Borgstein, MD[6]

INTRODUCTION: **Linaclotide improves abdominal pain and constipation in patients with constipation-predominant irritable bowel syndrome (IBS-C). Patients report additional bothersome abdominal symptoms of bloating and discomfort. The intention of this study was to evaluate linaclotide's efficacy in relieving IBS-C-related abdominal symptoms (bloating, discomfort, and pain) using a novel multi-item Abdominal Score (AS).**



[1]David Geffen School of Medicine at UCLA, Los Angeles, California, USA; [2]Mayo Clinic, Jacksonville, Florida, USA; [3]University of North Carolina, Atrium Health, Charlotte, North Carolina, USA; [4]Northwestern Medicine Digestive Health Center, Chicago, Illinois, USA; [5]AbbVie Inc, Madison, New Jersey, USA; [6]Formerly Employed at Ironwood Pharmaceuticals, Inc, Boston, Massachusetts, USA; [7]Ironwood Pharmaceuticals, Inc, Boston, Massachusetts, USA; [8]Formerly Employed at AbbVie Inc, Madison, New Jersey, USA; [9]Cyclerion Therapeutics, Cambridge, Massachusetts, USA.

The study was designed, conducted, and reported in compliance with Good Clinical Practices. Institutional review board-approved informed consent was reviewed and signed by all patients before commencing study participation. **Correspondence:** Lin Chang, MD. E-mail: LinChang@mednet.ucla.edu.

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METHODS: **Patients with IBS-C with abdominal pain ≥3 (0–10 scale) were randomized to linaclotide 290 μg or placebo daily for 12 weeks. The AS, derived from the Diary for IBS Symptoms-Constipation, is the average of abdominal bloating, discomfort, and pain at their worst (0 = none, 10 = worst possible). The primary end point was overall change from baseline (CFB) in AS. Secondary end points included CFB in 12-week AS evaluated using cumulative distribution function and 6-week/12-week AS responder (AS improvement ≥2 points for ≥6-week/12-week).**

RESULTS: **Overall, 614 patients (mean age 46.7 years; 81% female) were randomized. All prespecified end points showed significant benefit of linaclotide vs placebo. The mean overall CFB AS reduction for linaclotide was −1.9 vs −1.2 for placebo ($P < 0.0001$); the 6-week/12-week AS responder rate was 40.5% for linaclotide vs 23.4% for placebo (odds ratio = 2.2 [95% confidence interval, 1.55–3.12; $P < 0.0001$]). Diarrhea was the most common treatment-emergent adverse event (linaclotide = 4.6%, placebo = 1.6%).**

DISCUSSION: **Linaclotide significantly reduced multiple abdominal symptoms important to patients with IBS-C (bloating, discomfort, and pain) compared with placebo, as measured by a novel multi-item AS. The AS, derived from the Diary for IBS Symptoms-Constipation, should be considered for use in future IBS-C clinical studies to measure clinically meaningful improvements beyond traditional end points.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C48, http://links.lww.com/AJG/C49, http://links.lww.com/AJG/C50, http://links.lww.com/AJG/C51, http://links.lww.com/AJG/C52

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INTRODUCTION

Recurrent abdominal pain is a cardinal symptom of irritable bowel syndrome (IBS), as detailed in the Rome IV diagnostic criteria. A recent study identified differences in the characteristics of abdominal pain among IBS subtypes and found that individuals with constipation-predominant IBS (IBS-C) have more frequent and bothersome abdominal pain compared with the other IBS subtypes (1). Patients with IBS-C also experience additional bothersome abdominal symptoms, including bloating and discomfort (2–4). The underlying mechanisms leading to abdominal symptoms are complex and not completely understood, although research investigating the pathophysiology and patient burden of abdominal symptoms has found that visceral hypersensitivity is linked to abdominal pain in patients with IBS (5,6). The symptom of bloating, particularly in the absence of distension, has also been associated with visceral hypersensitivity (6,7). Similar to abdominal pain, abdominal bloating and discomfort affect patients' health-related quality of life (HRQoL) (8,9).

Linaclotide is a guanylate cyclase (GC)-C agonist, approved by the US Food and Drug Administration (FDA) in 2012 for treating IBS-C and chronic idiopathic constipation in adults (10). Linaclotide has 2 distinct mechanisms that alleviate IBS-C–associated bowel and abdominal symptoms. By binding to GC-C receptors in intestinal epithelium, linaclotide stimulates production of intracellular cyclic guanosine-3′,5′ monophosphate (cGMP), which is linked to increased luminal secretion and accelerated transit (11–14). In addition, in rodent models of colonic hypersensitivity, linaclotide exhibits analgesic effects by a distinct pathway whereby cGMP is secreted into intestinal submucosa and is linked to inhibition of colonic nociceptors, resulting in peripheral analgesia (15,16). This extracellular cGMP pathway in the submucosa functions independently from improvements in bowel transit and stool form (15,17,18).

The efficacy of linaclotide in relieving abdominal symptoms important to patients has not been fully evaluated. The primary end point in pivotal phase 3 trials of linaclotide in IBS-C (19,20) was a composite responder end point as recommended by the US FDA guidance for evaluating products to manage IBS, incorporating improvement in abdominal pain and increases in frequency of complete spontaneous bowel movements (CSBMs) (21). This composite responder end point preceded the extensive and rigorous patient-reported outcomes (PRO) research that identified the key abdominal symptoms central to the experience of patients with IBS-C and supported the development of a new PRO instrument, the Diary for IBS Symptoms-Constipation (DIBSS-C), which could be used as a primary end point in IBS-C trials to evaluate these symptoms (2).

The DIBSS-C was developed by the IBS Working Group of the Critical Path Institute's PRO Consortium (2) and is a patient-centric measure of bowel and abdominal symptoms developed in accordance with good measurement principles, as outlined in the US FDA PRO guidance, to assess core signs and symptoms of IBS-C in clinical trials (22). The PRO research supporting the DIBSS-C identified 3 key abdominal symptoms that patients consider most meaningful and important for a treatment to improve: bloating (identified as the most bothersome), discomfort, and pain (2). The Abdominal Score (AS) is a novel end point derived from the DIBSS-C. The validity, reliability, and responsiveness to change of the DIBSS-C AS were confirmed in a phase 2B study in IBS-C (23). This randomized, placebo-controlled, double-blind phase 3B study was designed to evaluate the efficacy of linaclotide in reducing IBS-C abdominal symptoms (bloating, discomfort, and pain) using the new DIBSS-C AS as the primary end point.

METHODS

Trial design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide 290 μg included patients with IBS-C at 78 centers in the United States. The first patient consented in June 2018 and the final patient's last visit was in April 2019. The study was designed, conducted, and reported in compliance with Good Clinical Practices. An institutional review board–approved informed consent form was reviewed and

signed by all patients before commencing the study participation (NCT03573908).

During initial screening (≤21 days), patients discontinued prohibited medications (e.g., anticholinergic agents, narcotics, and laxatives). Eligible patients entered the baseline period (14–21 days), during which they used a handheld electronic diary (eDiary) to record daily and weekly symptom severity. Eligible patients were randomized 1:1 to linaclotide 290 μg or placebo. At the end of 12 weeks, patients entered a 4-week randomized withdrawal period (RWP): patients who had been receiving linaclotide were rerandomized to linaclotide 290 μg or placebo (1:1); placebo patients were allocated to linaclotide 290 μg (see Figure, Supplementary Digital Content 1, http://links.lww.com/AJG/C48). The treatment period randomization list identified each patient by randomization number and included the patient's corresponding treatment assignment. The RWP list was stratified by the treatment assigned in the treatment period and included the stratum, patient's rerandomization number, and the corresponding treatment assignment. Randomization numbers were generated by Allergan (assigned by an interactive web response system). The patient retained the same identification number (which was also the screening number) throughout the treatment period.

For the double-blind treatment period and RWP, patients were supplied with identically appearing oral capsules containing linaclotide 290 μg or placebo. In addition to the daily and weekly eDiary assessments, patients completed site visits at weeks 4, 8, 12, and 16 (see Figure, Supplementary Digital Content 2, http://links.lww.com/AJG/C49).

Study patients

Eligible patients were men or women; ≥18 years; met Rome III IBS criteria (24); had stool consistency (Bristol Stool Form Scale score: 1 = hard/lumpy; 7 = liquid (25)) ≤2 for ≥25% of bowel movements (BMs) and ≥6 for <25% of BMs in the absence of antidiarrheal drugs or laxatives; reported <3 spontaneous BMs (SBMs) per week for ≥12 weeks; and reported the following in the 2 weeks before randomization: average abdominal pain at its worst of ≥3 (11-point numerical rating scale: 0 = none; 10 = worst possible); ≤6 CSBMs (SBMs associated with a sense of complete evacuation); and ≤10 SBMs. Specified rescue medications were allowed during pretreatment but not on the day before or the day of randomization.

Efficacy assessments and end points

Patients reported each BM through the eDiary, including stool consistency using the Bristol Stool Form Scale and straining (5-point scale: 1 = not at all; 5 = an extreme amount). Any BMs recorded the day of or the day after rescue medication (bisacodyl, allowed ≥72 hours since previous BM or for intolerable symptoms) were not counted as an SBM or CSBM. Patients reported daily assessments for abdominal bloating, discomfort, and pain each assessed at their worst (11-point numerical rating scale: 0 = none; 10 = worst possible); weekly assessments of constipation severity and general IBS symptom severity (1 = none; 5 = very severe), and adequate relief of symptoms (yes/no).

Daily ASs were calculated by averaging daily assessments of abdominal bloating, discomfort, and pain. Weekly ASs were calculated by averaging daily ASs from a given week. Daily ASs were considered missing if ≥2 abdominal symptom assessments were not reported.

The primary efficacy end point for this study was the change from baseline (CFB) in weekly AS throughout the treatment period. The 2 secondary efficacy end points were also based on the weekly AS: the CFB in 12-week AS (average of daily ASs from the 12-week treatment period) determined using a cumulative distribution function (CDF) and the 6-week/12-week AS responder, defined as a patient who experienced ≥2-point reduction from baseline in weekly AS for ≥6 of the 12 treatment weeks.

Additional end points included CFB in individual abdominal symptoms (bloating, discomfort, and pain), percentage of days with use of rescue medicine, the 6-week/12-week responders for combined abdominal pain and constipation (weekly increase from baseline of ≥1 CSBM and a decrease from baseline of ≥30% in the respective weekly abdominal pain score), and treatment satisfaction (see Table, Supplementary Digital Content 3, http://links.lww.com/AJG/C50).

Safety assessments

The site investigator assessed all adverse events (AEs) and serious AEs and determined their severity and relationship to study treatment during the study period; reports were taken at each visit (i.e., weeks 4, 8, 12, and 16). Other safety assessments included standard clinical laboratory measures, body weight, and vital sign measurements.

Statistical methods and data analysis

The primary efficacy end point (overall CFB in AS throughout treatment) was evaluated using a mixed model with repeated measures (MMRM) framework, with week, treatment, geographic region, and week-by-treatment as the fixed effects, patient as the random effect, and baseline value as the covariate. A secondary time-course analysis of the primary end point (CFB in AS) used the above-described MMRM framework to assess treatment difference at individual weeks. Results at weeks 12, 10, 8, 6, 4, 2, and 1 were part of the multiplicity control in the testing hierarchy. Descriptive statistics based on the MMRM for the overall CFB throughout treatment and CFBs at individual weeks included the least squares mean difference (linaclotide 290 μg vs placebo), 95% confidence intervals (CIs), and the *P* value associated with the treatment comparison.

For CFB in the 12-week AS (12-week score minus the baseline score), the CDFs for linaclotide and placebo were estimated. Distributions of CFB in the 12-week AS were compared using the Wilcoxon rank sum test with Hodges-Lehmann estimator for the median difference.

For the 6-week/12-week AS, the proportion of responders in the linaclotide 290 μg and placebo groups were compared using a Cochran-Mantel-Haenszel test controlling for geographic region. The number and percentage of responders, the difference in responder rates between the linaclotide and placebo groups, the odds ratio relative to placebo, all corresponding 95% CIs, and the *P* value associated with the Cochran-Mantel-Haenszel test were noted.

To control for multiplicity, the overall family-wise type I error rate for the primary and secondary efficacy analyses was controlled at the $\alpha = 0.05$ level by using a fixed-sequence testing procedure. Additional continuous efficacy end points were analyzed using the same MMRM methods as the primary end point, and additional responder efficacy end points were analyzed in a similar way to secondary responder end points but

explored outside of the formal testing procedures and not controlled for multiplicity.

The sample size of 600 patients (300 patients per treatment group) was chosen to ensure adequate power for testing the fixed-sequence procedure for the primary and secondary efficacy end points. The power calculations for the primary end point were based on the placebo and linaclotide 290 μg treatment groups from the phase 3 trial (20). The patients in the phase 3 trial were considered representative of the patient population for this trial. Using a resampling with replacement-based simulation (1,000 iterations) and controlling for multiplicity, the trial had >99% power to reject the primary end point and ~94% power to reject all primary and secondary hypotheses defined in the testing process.

RESULTS

Patient disposition, demographics, and baseline characteristics

Of the 1,045 patients screened, 614 were randomized and received ≥1 dose of the study drug; 564 (91.9%) completed 12 weeks of treatment. The treatment groups were well-balanced regarding demographics and baseline symptoms (Table 1).

Compliance with eDiary completion was similar between treatments with limited change across the 12 weeks. At week 1, 86.0% of linaclotide and 88.9% of placebo patients completed ≥80% of the daily eDiary; at week 12, those percentages were 84.7% and 84.0%, respectively. Overall, the mean treatment compliance rate was approximately 97% in both treatment groups.

Efficacy results

The overall AS reduction was significantly greater for linaclotide-treated patients compared with that for placebo (mean CFB: −1.9 vs −1.2; $P < 0.0001$; Table 2). Reduction from baseline in AS was significantly greater for linaclotide compared with placebo starting at week 1; differences were statistically significant for all prespecified analysis time points using the fixed-sequence testing procedure ($P < 0.0005$ for all linaclotide comparisons vs placebo; Figure 1 and Table 2). The changes reached a plateau at week 8 for placebo but continued to decrease for the remaining 4 weeks with linaclotide.

The CDF plots for the 12-week CFB in AS showed that greater proportions of linaclotide-treated patients had a reduction compared with the placebo group; the difference between the linaclotide and placebo distribution curves was statistically significant ($P < 0.0001$; Figure 2). The plots showed consistent separation of the linaclotide and placebo groups in AS reductions ranging from <0 to −9, with the greatest separation at thresholds of −1 to −4.

Of the linaclotide-treated patients, 40.5% were 6-week/12-week AS responders, compared with 23.4% with placebo (odds ratio = 2.2; 95% CI, 1.55–3.12; $P < 0.0001$). All primary and secondary end point comparisons of linaclotide vs placebo were statistically significant (Table 2).

Reductions in key abdominal symptoms–bloating, discomfort, and pain–seemed similar to the reductions in AS (mean CFB vs placebo: −1.9 vs −1.1, −1.9 vs −1.2, −1.9 vs −1.2, respectively; $P < 0.0001$ for each [see Table, Supplemental Digital Content 3, http://links.lww.com/AJG/C50]). CFB for abdominal bloating showed reductions for the linaclotide-treated patients at each week for 12 weeks ($P \leq 0.0001$ for all comparisons; Figure 3). Similarly, CFB for abdominal discomfort and pain showed reductions at each week for 12 weeks ($P \leq 0.0005$ for all linaclotide vs placebo comparisons; Figure 3).

The combined abdominal pain and constipation responder end point showed a higher response rate for the linaclotide-treated patients compared with the placebo group (29.4% vs 16.9%; $P < 0.001$). All additional end points showed benefit for linaclotide ($P < 0.0001$), with the exception of CFB in percentage of days with use of rescue medicine ($P = 0.1632$) (see Table, Supplementary Digital Content 3, http://links.lww.com/AJG/C50).

AS and bowel symptom data in the RWP demonstrated that patients with continued linaclotide dosing had a persistent treatment response, whereas patients who shifted from linaclotide to placebo had a diminished treatment response (see Table, Supplementary Digital Content 4, http://links.lww.com/AJG/C51).

Safety

During the treatment period, the incidence of treatment-emergent AEs (TEAEs) in the linaclotide and placebo groups

Table 1. Patient demographics and baseline characteristics

Characteristic	Placebo (N = 308)	Linaclotide (N = 306)
Age (yr), mean (range)	46.8 (18–79)	46.5 (19–85)
≥65 yr, n (%)	36 (11.7)	33 (10.8)
Women, n (%)	255 (82.8)	241 (78.8)
Race, n (%)		
White	198 (64.3)	189 (61.8)
Black	70 (22.7)	76 (24.8)
Asian	35 (11.4)	36 (11.8)
Other	5 (1.6)	5 (1.6)
BMI, mean (SD)	29.39 (6.51)	29.50 (6.88)
Previous GC-C agonist exposure, n (%)[a]	69 (22.4)	64 (20.9)
Baseline efficacy values, mean (SD)		
Abdominal Score	6.46 (1.60)	6.39 (1.63)
Bloating	6.64 (1.70)	6.56 (1.71)
Discomfort	6.47 (1.64)	6.39 (1.64)
Pain	6.26 (1.66)	6.22 (1.69)
CSBMs/wk	0.26 (0.53)	0.27 (0.51)
SBMs/wk	1.60 (1.09)	1.72 (1.11)
BSFS score	2.11 (0.88)	2.19 (0.94)
IBS symptom severity[b]	3.62 (0.68)	3.59 (0.70)
Constipation severity[b]	3.72 (0.63)	3.71 (0.73)

BMI, body mass index; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; GC-C, guanylate cyclase-C; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; SBM, spontaneous bowel movement.

[a]Patients who reported previous treatment with linaclotide or plecanatide (both are GC-C agonists approved to treat IBS-C) were allowed to enter the study after a 30-day medication washout.

[b]Assessed on a scale of 1–5 (1 = none; 5 = very severe).

Table 2. Overview of efficacy results (primary and secondary end points)

	Fixed sequence for testing	Placebo	Linaclotide	*P* value[a]
1	CFB in weekly Abdominal Score–overall treatment effect, LS mean (SE)	−1.182 (0.109)	−1.898 (0.111)	<0.0001
2	CFB in the 12-wk Abdominal Score–cumulative distribution[b]	—	—	<0.0001
3	The 6-wk/12-wk Abdominal Score responder, %[c]	23.4	40.5	<0.0001
CFB in weekly Abdominal Score, LS mean (SE)				
4	At wk 12	−1.480 (0.133)	−2.347 (0.135)	<0.0001
5	At wk 10	−1.478 (0.130)	−2.197 (0.132)	<0.0001
6	At wk 8	−1.446 (0.130)	−2.110 (0.131)	0.0002
7	At wk 6	−1.183 (0.122)	−2.014 (0.124)	<0.0001
8	At wk 4	−1.048 (0.115)	−1.731 (0.117)	<0.0001
9	At wk 2	−0.795 (0.102)	−1.423 (0.104)	<0.0001
10	At wk 1	−0.490 (0.085)	−0.925 (0.087)	<0.0001

LS means, SEs, LSMDs, and *P* values were obtained based on an MMRM with treatment, analysis week, geographic region, and treatment-by-week interactions as fixed effects and baseline score as a covariate.
CFB, change from baseline; LS, least squares; LSMD, least squares mean difference; MMRM, mixed model with repeated measures.
[a]*P* values met the criteria for statistical significance under the fixed-sequence testing procedure.
[b]The cumulative distribution function plot of CFB in the 12-week Abdominal Score is shown in Figure 2.
[c]Based on a 2-point improvement on the Abdominal Score.

was 31.0% and 26.6%, respectively (Table 3). Overall, 9 (2.9%) linaclotide-treated and 4 (1.3%) placebo-treated patients discontinued treatment because of AEs.

Diarrhea was the most frequently reported TEAE among linaclotide-treated patients, reported by 14 patients (4.6%) receiving linaclotide and 5 (1.6%) receiving placebo. Of the 14 linaclotide-

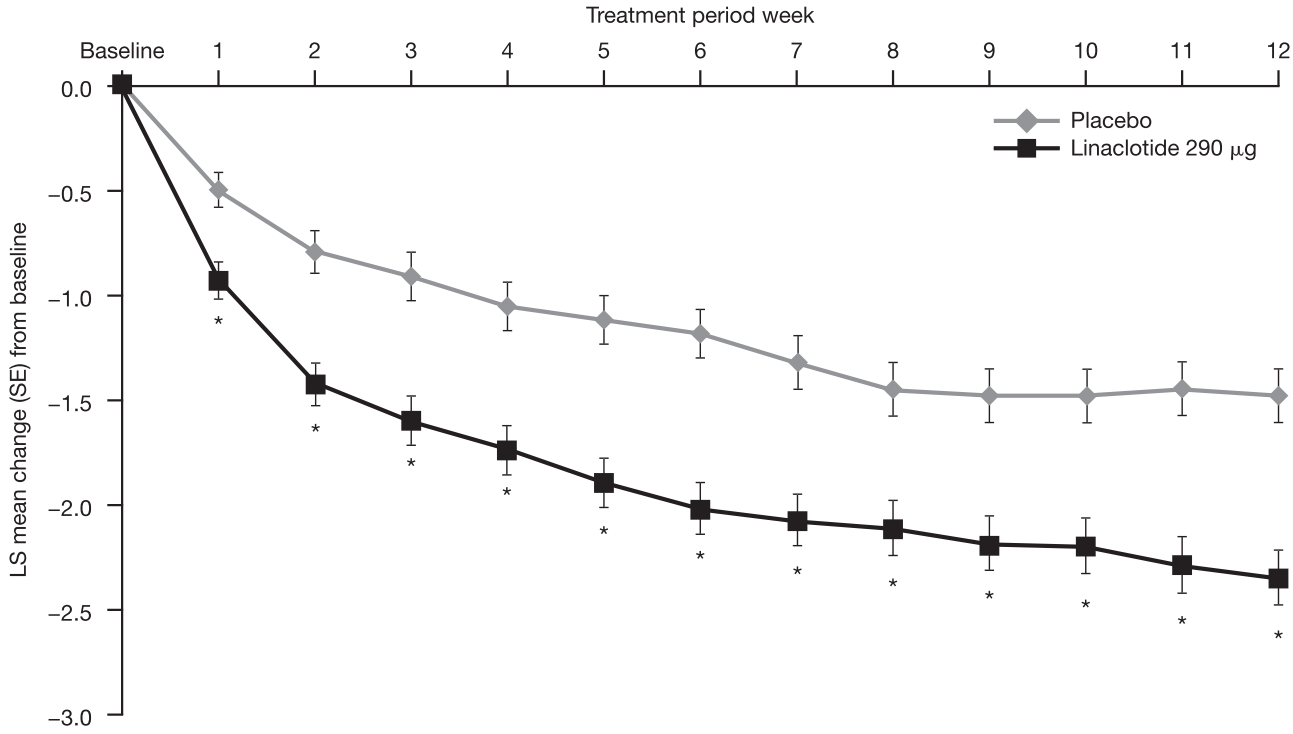

Figure 1. Change from baseline in LS mean Abdominal Score at each week during the treatment period. *$P \leq 0.0002$ ($P < 0.0001$ for all linaclotide comparisons vs placebo except week 8 [$P = 0.0002$]), based on LS mean CFB. LS means were obtained based on a mixed model with repeated measures, with treatment, analysis week, geographic region, and treatment-by-week interactions as fixed effects and baseline score as a covariate. CFB, change from baseline; LS, least squares.

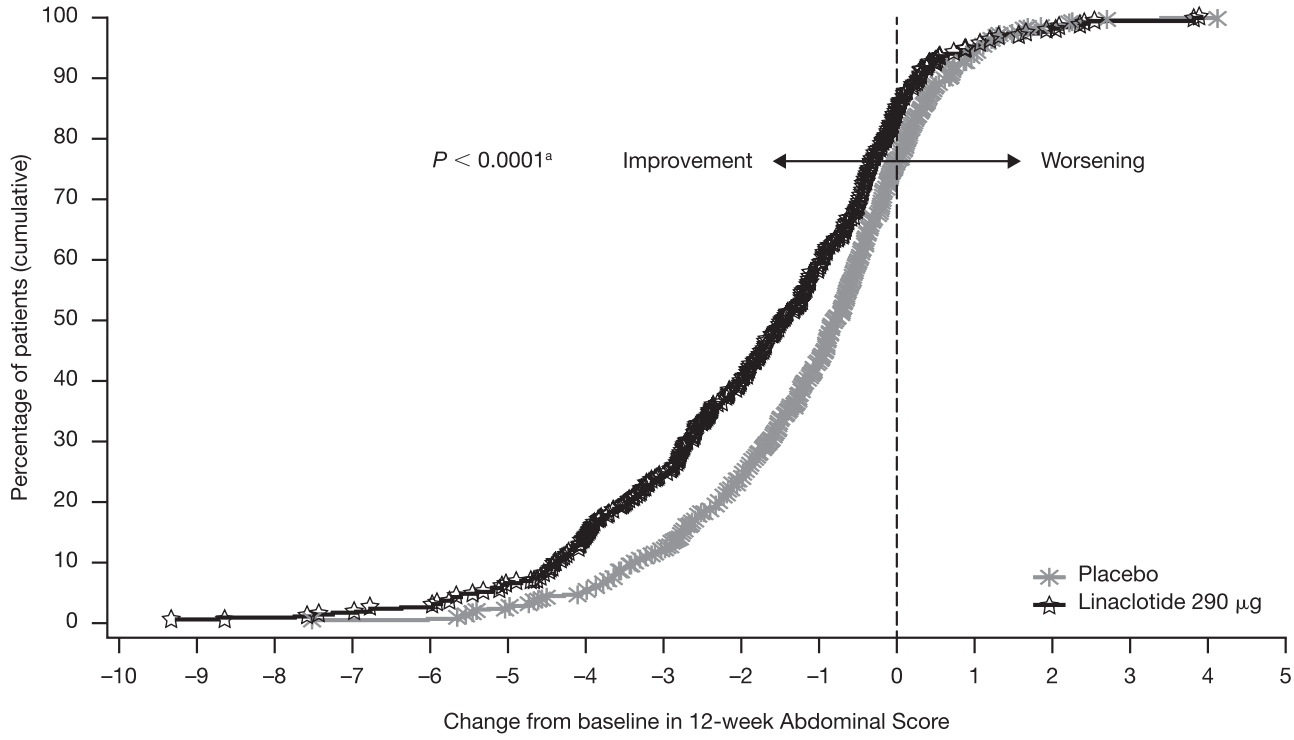

Figure 2. Change from baseline in the 12-week Abdominal Score by cumulative distribution function. Cumulative distribution function; each plotted point represents a single patient, with the y value for that point representing the cumulative percentage of patients with ≤ change from baseline on the x axis. [a]*P* value comparing change from baseline distributions by treatment obtained from Wilcoxon rank sum test. *P* value met the criteria for statistical significance under the fixed-sequence testing procedure.

treated patients, 2 (0.7%) experienced severe diarrhea, 4 (1.3%) moderate, and 8 (2.6%) mild. No patients had diarrhea as a serious AE. Discontinuations due to diarrhea occurred in 5 linaclotide-treated patients (1.6%) and none in the placebo group. Exploratory analyses found no correlations between diarrhea TEAE and previous GC-C exposure.

Four patients (1.3%) in the linaclotide group and 2 patients (0.6%) in the placebo group reported at least 1 serious AE; none were considered related to the study treatment (see Table, Supplementary Digital Content 5, http://links.lww.com/AJG/C52). No deaths were reported.

During the RWP, TEAEs occurred in 10.1% of linaclotide-linaclotide patients, 10.2% of linaclotide-placebo patients, and 18.3% of placebo-linaclotide patients. Diarrhea occurred in 2.2% of linaclotide-linaclotide patients, 1.5% of linaclotide-placebo patients, and 5.7% of placebo-linaclotide patients. Incidence of other TEAEs during the period was similar across the 3 treatment sequences. No patients in the linaclotide-placebo sequence experienced worsening in symptoms relative to baseline during this period.

DISCUSSION

This is the first large phase 3 clinical trial using a novel patient-centric measure of IBS-C symptoms, the DIBSS-C AS, to evaluate the efficacy of a pharmacologic intervention in reducing abdominal bloating, discomfort, and pain in patients with IBS-C. Linaclotide was associated with a significantly greater reduction from baseline in AS compared with placebo for the overall treatment period. Differences from placebo at each of the 12 weeks were significant ($P \leq 0.0002$) and ranged from 0.435 at week 1 to 0.867 at week 12. Linaclotide was associated with significant reductions in individual abdominal bloating, discomfort, and pain symptoms vs placebo in the first week, followed by progressive reductions through 12 weeks of the treatment period and sustained in the linaclotide-treated patients who continued on linaclotide through week 16 (end of the RWP).

The clinical relevance of the treatment difference using the AS may be best understood by considering the primary end point results–both the primary and secondary analyses of the end point–in conjunction with the overall magnitude of change in AS. For linaclotide-treated patients, the mean CFB in AS surpassed the −2.0 threshold at week 6, whereas for placebo-treated patients, it did not cross the −2.0 threshold during the 12-week treatment period. Furthermore, 40.5% of linaclotide-treated patients achieved a ≥2.0-point decrease in AS for at least 6 of the 12 weeks of treatment when compared with 23.4% in the placebo group ($P < 0.0001$). Based on psychometric analyses of clinical trial data, a 2.0-point change in the AS was determined to be an appropriate threshold for identifying meaningful within-patient change (23). However, a threshold of 2.5 points was ultimately selected after interaction with the US FDA and is reflected in the linaclotide prescribing information, with a treatment difference of 15.5% (95% CI, 8.6%–22.3%) (10).

Patients with IBS-C experience multiple important and bothersome bowel and abdominal symptoms, including infrequent BMs, straining, abdominal bloating, discomfort, and pain (3). Although abdominal pain and discomfort are defining features of IBS (4,24), with pain driving increases in overall IBS severity and healthcare visits and decreases in HRQoL (26), abdominal bloating is reported in up to 75% of patients, with

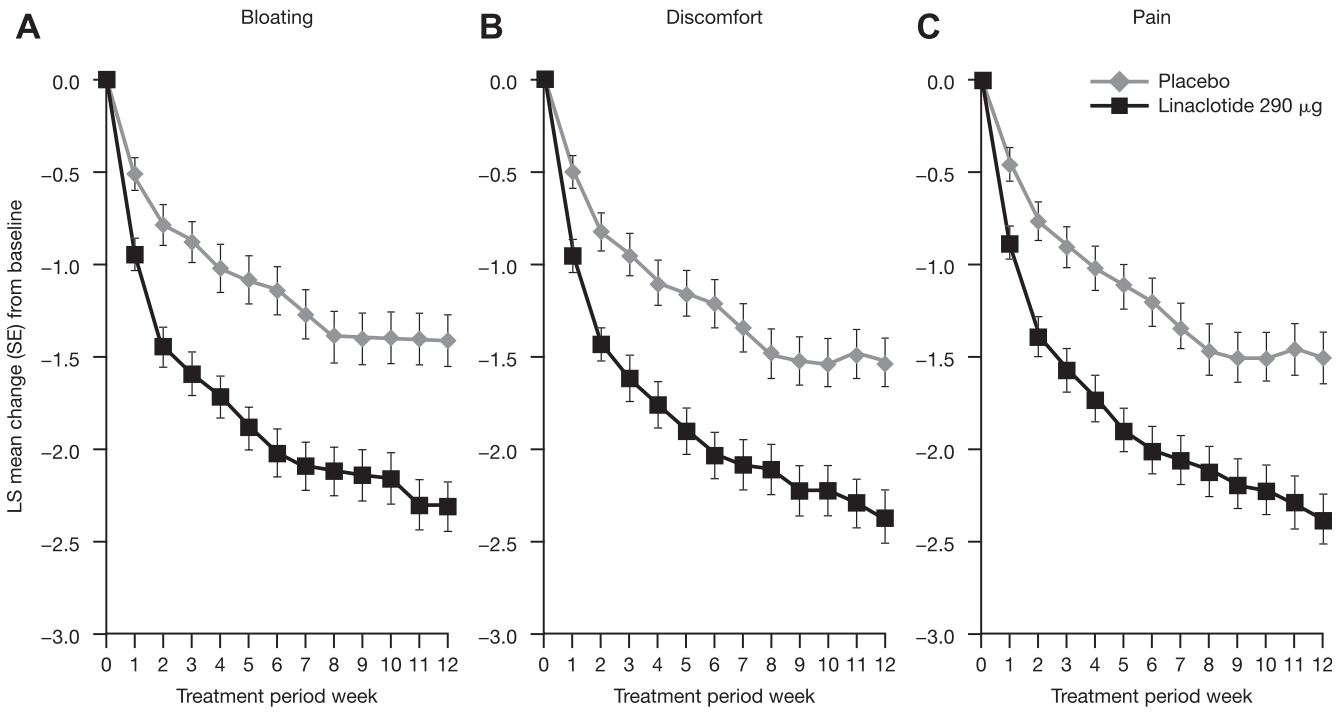

Figure 3. Individual abdominal symptom results: abdominal bloating, discomfort, and pain. Nominal $P \leq 0.0001$ for all linaclotide comparisons vs placebo, except week 8 for abdominal pain ($P = 0.0002$) and discomfort ($P = 0.0005$) based on a mixed model with repeated measures, with treatment, analysis week, geographic region, and treatment-by-week interactions as fixed effects and baseline score as a covariate. LS, least squares.

most reporting moderate to severe bloating with effects on HRQoL (7). A recent study found that pain and bloating in IBS contribute to medication risk-taking behavior (27). Furthermore, these abdominal symptoms can be manifestations of visceral hypersensitivity, a hallmark IBS characteristic. Multiple studies have demonstrated decreased abdominal pain and discomfort thresholds in response to balloon distension in the rectum and colon of patients with IBS compared with healthy controls (28–32). In addition, abdominal pain and bloating are the 2 IBS symptoms that are associated with increased rectal perception in IBS (31).

Table 3. TEAEs reported in >1% of the linaclotide-treated patients during the treatment period

Adverse event (preferred term)	Placebo (N = 308), n (%)	Linaclotide (N = 306), n (%)
Patients with at least 1 TEAE	82 (26.6)	95 (31.0)
Diarrhea	5 (1.6)	14 (4.6)
Headache	3 (1.0)	8 (2.6)
Abdominal pain[a]	7 (2.3)	7 (2.3)
Nausea	5 (1.6)	6 (2.0)
Upper respiratory tract infection	4 (1.3)	6 (2.0)
Nasopharyngitis	9 (2.9)	5 (1.6)
Abdominal distension	4 (1.3)	4 (1.3)
Cough	3 (1.0)	4 (1.3)
Urinary tract infection	3 (1.0)	4 (1.3)

N, number of patients in the safety population; n, number of patients with TEAEs within a specific category; TEAE, treatment-emergent adverse event.
[a]Abdominal pain includes the preferred terms "abdominal pain," "abdominal pain upper," and "abdominal pain lower."

Several different global and symptom-specific PRO measures have been used to support approval of treatments for IBS. However, the US FDA has consistently emphasized the need for a comprehensive patient-centric measure in line with expectations described in its PRO guidance (22) that includes patient assessments of stool consistency, bowel function, and abdominal symptom severity to best capture the complete patient experience and measure treatment response in IBS-C clinical trials (21). The DIBSS-C was developed by the IBS Working Group of the Critical Path Institute's PRO Consortium, in collaboration with a patient advocacy organization, clinical experts, measurement experts, and input from the US FDA to support the construction of primary and secondary end points in IBS-C clinical trials under the US FDA's Drug Development Tool qualification program. To assess core abdominal symptoms important to patients withIBS-C, AS was derived from the 3 abdominal symptom items of the DIBSS-C (bloating, discomfort, and pain). Psychometric analyses provide evidence of reliability, validity, responsiveness, and interpretability of the DIBSS-C AS for assessing treatment benefit in IBS-C clinical trials (23).

Given recent research that found that the presentation and characteristics of abdominal symptoms differ among the IBS subtypes (1), the DIBSS-C, developed and validated for use in patients with the IBS-C subtype, will prove useful in future clinical trials evaluating symptom improvement in patients with IBS-C. Importantly, the AS allows for the assessment of abdominal symptom relief independent of BM relief and clinically meaningful assessment of 2 key symptoms endorsed as important to patients with IBS-C–abdominal bloating and discomfort–both

not previously captured by the US FDA-recommended primary end point (21). In yielding the multi-item AS, the DIBSS-C is an important, novel tool for evaluating the efficacy of linaclotide in relieving the key abdominal symptoms of bloating, discomfort, and pain. The safety profile of linaclotide during this study was consistent with previous results, although the rate of diarrhea was lower than that reported in previous linaclotide studies in IBS-C (19,20). In addition, symptoms did not worsen relative to baseline in the RWP.

This trial enrolled patients with IBS-C based on the Rome III diagnostic criteria for consistency with the validating trial for the DIBSS-C (23,33). Patient information relevant to the Rome IV criteria were also collected. An assessment of the enrolled patients showed that 613 of the 614 patients also met the Rome IV criteria. More than 80% of the patients enrolled in this trial were women; although this is higher than estimates of the percentage of female patients with IBS-C (34), it is consistent with earlier linaclotide trials in IBS-C (19,20) and with the increased likeliness of women to seek health care for IBS compared with men by a ratio of 2.5:1 (35).

Compared with placebo, linaclotide significantly improved multiple IBS-C abdominal symptoms identified by patients as bothersome and important for a treatment to improve (abdominal bloating, discomfort, and pain), with reported AEs consistent with the established safety profile. This phase 3B trial using the novel DIBSS-C AS demonstrated the efficacy of linaclotide beyond the traditional symptoms of BMs and abdominal pain, with results indicating linaclotide can be used effectively as a single pharmacologic approach in the management of IBS-C-associated abdominal symptoms.

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CONFLICTS OF INTEREST

Guarantor of the article: Wilmin Bartolini, PhD.

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Study Highlights

WHAT IS KNOWN

- ✓ Abdominal pain, in conjunction with disordered defecation, defines irritable bowel syndrome (IBS).
- ✓ Patients with constipation-predominant IBS often experience additional bothersome abdominal symptoms, including bloating and discomfort.
- ✓ To fully characterize constipation-predominant IBS treatment effects on abdominal symptoms, an appropriately developed patient-reported outcome instrument is needed.

WHAT IS NEW HERE

- ✓ The Diary for IBS Symptoms-Constipation (DIBSS-C) is a new patient-reported outcome instrument.
- ✓ DIBSS-C is inclusive of the Abdominal Score assessing bloating, discomfort, and pain severity.
- ✓ This is the first large randomized controlled trial evaluating constipation-predominant IBS treatment efficacy using the DIBSS-C.
- ✓ Linaclotide showed overall benefit for key abdominal symptoms (bloating, discomfort, and pain) compared with placebo.

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