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Linaclotide for Irritable Bowel Syndrome With Constipation: A 26-Week, Randomized, Double-blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety

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OBJECTIVES: **Linaclotide is a minimally absorbed peptide guanylate cyclase-C agonist. The objective of this trial was to determine the efficacy and safety of linaclotide treatment in patients with irritable bowel syndrome with constipation (IBS-C) over 26 weeks.**

METHODS: **This phase 3, double-blind, parallel-group, placebo-controlled trial randomized IBS-C patients to placebo or 290 μg of oral linaclotide once daily for a 26-week treatment period. The primary and the secondary efficacy assessments were evaluated over the first 12 weeks of treatment. Primary end points included the Food and Drug Administration's (FDA's) end point for IBS-C (responder: a patient who reported (i) improvement of ≥30% from baseline in average daily worst abdominal pain score and (ii) increase of ≥1 complete spontaneous bowel movement (CSBM) from baseline, both in the same week for ≥6/12 weeks) and three other primary end points, based on improvements in abdominal pain and CSBMs for 9/12 weeks. Adverse events (AEs) were monitored.**

RESULTS: **In all, 804 patients (mean age = 44 years, female = 90%, white = 78%) were evaluated; 33.7% of linaclotide-treated patients were FDA end point responders, vs. 13.9% of placebo-treated patients ($P < 0.0001$) (number needed to treat = 5.1, 95% confidence interval (CI): 3.9, 7.1). The pain responder criterion of the FDA end point was met by 48.9% of linaclotide-treated patients vs. 34.5% of placebo-treated patients (number needed to treat = 7.0, 95% CI: 4.7, 13.1), and the CSBM responder criterion was met by 47.6% of linaclotide-treated patients, vs. 22.6% of placebo patients (number needed to treat = 4.0, 95% CI: 3.2, 5.4). Remaining primary end points ($P < 0.0001$) and all secondary end points ($P < 0.001$), including abdominal pain, abdominal bloating, and bowel symptoms (SBM and CSBM rates, Bristol Stool Form Scale (BSFS) score, and straining), were also statistically significantly improved with linaclotide vs. placebo. Statistically significant differences from placebo were observed for responder and continuous end points over 26 weeks of treatment. AE incidence was similar between treatment groups, except for diarrhea, which caused discontinuation in 4.5% of linaclotide patients vs. 0.2% of placebo patients.**

CONCLUSIONS: **Linaclotide 290 μg once daily significantly improved abdominal and bowel symptoms associated with IBS-C over 26 weeks of treatment.**

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain or discomfort associated with altered defecation (1). IBS affects ~7–15% of the population in North America (2,3), and ~11.5% of the European population (4). IBS with constipation (IBS-C) negatively

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impacts quality of life in those affected (5), and places a significant financial burden on society through reduced work productivity and increased use of health-related resources (6).

IBS is subclassified based on the predominant alteration in stool form: IBS-C, IBS with diarrhea, mixed IBS, and unsubtyped IBS (1). Up to one-third of IBS patients have IBS-C (5). In addition to abdominal pain or discomfort and reduced stool frequency, IBS-C patients also report a number of other complaints including bloating, hard stools, straining, and a sensation of incomplete evacuation (7).

Linaclotide, a minimally absorbed, 14-amino acid peptide guanylate cyclase-C agonist structurally related to the endogenous guanylin peptide family, binds to and activates GC-C on the luminal surface of the intestinal epithelium. Activation of GC-C results in generation of cyclic guanosine monophosphate (cGMP), which is increased both intracellularly and extracellularly. The increase in cGMP within intestinal epithelial cells triggers a signal transduction cascade activating the cystic fibrosis transmembrane conductance regulator (8). This activation causes secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased luminal fluid secretion and an acceleration of intestinal transit. In several animal models, linaclotide treatment has accelerated gastrointestinal transit and reduced visceral nociception (8,9). cGMP also reduced the firing of afferent pain fibers when applied to the colonic mucosa isolated from mice with visceral hypersensitivity (10); presumably, extracellular cGMP mediates visceral analgesia by modulating the activity of such pain fibers *in vivo*. In humans, linaclotide accelerated colonic transit and improved abdominal pain and constipation associated with IBS-C (11,12).

The objective of the current phase 3 clinical trial was to assess the efficacy and safety of linaclotide at a dosage of 290 µg vs. placebo administered once daily for 26 weeks to patients with IBS-C. The choice of efficacy end points for IBS clinical trials assessing new therapeutic agents has evolved over the past few years. Traditional primary global assessment end points have been supplanted by responder end points based on symptoms that are important and bothersome to patients and developed according to the 2009 Food and Drug Administration (FDA) patient-reported outcome guidance (13). Recognizing that the development and validation of a content-valid patient-reported outcome instrument for IBS could be protracted, the FDA provided recommendations for primary end points for provisional use in IBS treatment trials in an IBS guidance document finalized in May 2012 (14). This linaclotide trial evaluated four primary responder end points, including the combined end point recommended by the FDA for IBS-C trials, as well as a number of secondary responder and change-from-baseline end points.

METHODS

Trial design

This 26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 102 clinical centers in the United States between July 2009 (first patient enrolled) and September 2010 (last patient completed). The trial was designed, conducted, and reported in compliance with the principles of Good Clinical Practice guidelines. At each center, an informed consent form approved by an Institutional Review Board was reviewed and signed by all patients before their participation in the trial.

During an initial screening period of up to 21 days, patients provided blood and urine for routine testing and were instructed to discontinue any prohibited medications (e.g., anti-cholinergics and narcotics) for at least 14 days (24 h for non-steroidal anti-inflammatory drugs, if taken for abdominal pain, and for laxatives) before the start of baseline assessments. Patients meeting the inclusion and exclusion criteria then entered the 14–21 day baseline period (with data from the last 14 days used to calculate baseline values), during which they used an interactive voice response system to provide daily and weekly symptom assessments. Patients eligible for the 26-week treatment period were randomized (1:1) to receive 290 µg linaclotide or placebo, administered as an oral capsule once daily at least 30 min before breakfast. This dose-strength designation reflects specific linaclotide content rather than the total peptide content expressed in some previously reported studies, as linaclotide content is a more accurate and precise indication of dose strength. The actual amount of linaclotide received by patients did not change during this trial or the linaclotide clinical program.

In addition to a screening visit, study site visits occurred at the start of the baseline period (day -14) and throughout the treatment period (days 1, 15, 29, 57, 85, 113, 141, and 183). All personnel involved in the design and implementation of the trial remained blinded until the database was locked.

Trial patients

Patients were men and women aged 18 years or older who met modified Rome II criteria for IBS-C (1). In the 12 months before the screening visit, eligible patients reported for at least 12 weeks, which need not be consecutive, abdominal pain or abdominal discomfort that had ≥2 of these three features: (i) relieved with defecation, (ii) onset associated with a change in frequency of stool, and/or (iii) onset associated with a change in form (appearance) of stool, before starting chronic treatment with tegaserod or lubiprostone (if patients had taken these medications); and < 3 spontaneous bowel movements (SBMs, defined as bowel movements (BMs) occurring in the absence of laxative, enema, or suppository use during the 24 h before the BM) per week and ≥1 of these symptoms: (i) straining during > 25% of BMs, (ii) lumpy or hard stools during > 25% of BMs, and (iii) a sensation of incomplete evacuation during > 25% of BMs, before starting chronic treatment with tegaserod, lubiprostone, polyethylene glycol 3350, or any laxative (if patients had taken these medications). To be eligible for randomization, patients had to report during the baseline period an average score of ≥3 for daily abdominal pain at its worst (worst abdominal pain) on an 11-point numeric rating scale (0 = no abdominal pain, 10 = severe abdominal pain), and an average of < 3 complete SBMs (CSBMs, defined as SBMs accompanied by patient self-reporting of a feeling of complete evacuation) per week and ≤5 SBMs/week.

Exclusion criteria included loose (mushy) or watery stools reported in the absence of laxatives for >25% of BMs during the 12 weeks preceding the trial; mushy stool (Bristol Stool Form Scale (BSFS) (15) score of 6) for >1 SBM, or a watery, liquid stool (BSFS score of 7) for any SBM during the baseline period; a history of surgery to remove a segment of the gastrointestinal tract or bariatric surgery for obesity at any time; appendectomy/cholecystectomy within 2 months or other abdominal surgeries within 6 months before entry into the trial; history of diverticulitis or any chronic condition that could be associated with abdominal pain or discomfort and could confound the assessments in this trial; or a history of laxative abuse. In general, patients were excluded if they were taking drugs that could cause constipation (e.g., narcotics); however, patients taking certain drugs for IBS that might be constipating (e.g., tricyclic antidepressants) were eligible provided that they were on a stable dose for at least 30 days before the screening visit and there was no plan to change the dose after the screening visit. Colonoscopy requirements were based on the American Gastroenterological Association guidelines (16).

Efficacy assessments and end points

Daily symptoms recorded using interactive voice response system included worst abdominal pain, abdominal discomfort, abdominal cramping, abdominal fullness, and abdominal bloating (all abdominal symptoms were measured using an 11-point numeric rating scale); the number of BMs and whether rescue medication (i.e., per protocol use of bisacodyl 5 mg tablets or 10 mg suppositories) was used. Each BM was assessed for sensation of complete bowel emptying (yes/no), stool consistency (7-point BSFS), and severity of straining (5-point ordinal scale). Weekly assessments included constipation severity, IBS severity (both using a 5-point ordinal scale), degree of IBS relief (7-point balanced scale), and adequate relief of IBS-C symptoms (yes/no). Assessment of satisfaction with the trial medication's ability to relieve IBS symptoms (treatment satisfaction) was captured at all visits following randomization.

Primary end points. Based on the recommendations for IBS-C trial design and provisional end points in the recently finalized FDA guidance for IBS clinical trials (May 2012) (14), a responder was defined as a patient who met both of the following criteria in the same week for at least 6 out of the first 12 weeks of the treatment period (to be referred to hereafter as "FDA end point"): (i) an improvement of ≥30% from baseline in the average of the daily worst abdominal pain scores and (ii) an increase of ≥1 CSBM from baseline. This combined end point was one of the four primary end points measured in the trial; it was added after the initiation of the trial, but before completion of enrollment and database lock, with a protocol amendment (no unblinding had occurred). The other three primary end points were also responder definitions, which required patients to meet the following weekly responder criteria for at least 9 out of the first 12 weeks of the treatment period: (i) an improvement of ≥30% from baseline in the weekly average of the daily worst abdominal pain scores, (ii) ≥3 CSBMs and an increase of ≥1 CSBM from baseline, and (iii) a combined end point that defined a responder as a patient who met criteria for both (i) and (ii) in the same week.

Secondary end points. The 12-week change-from-baseline secondary end points included: worst abdominal pain, abdominal discomfort, abdominal bloating, stool frequency (CSBM and SBM weekly rates), stool consistency (BSFS), and severity of straining. Efficacy parameters measured as primary and secondary end points were also evaluated over 26 weeks of treatment as additional end points, and a number of other additional end points were assessed, including 12-week and 26-week change-from-baseline end points for abdominal fullness and abdominal cramping, abdominal- and bowel-symptom responders, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, and treatment satisfaction.

Safety assessments

The site investigator assessed all patient-reported adverse events (AEs) and serious AEs (SAEs) and determined their severity and relationship to study treatment. Other safety evaluations included physical examinations, electrocardiogram recordings, vital sign measurements, and standard clinical laboratory tests.

Pharmacokinetic assessments

During the treatment period, a subset of patients had blood samples taken at the randomization and week 4 visits to determine if linaclotide or its active metabolite, MM-419447, could be detected at quantifiable levels in the plasma.

Statistical methods and data analysis

Patients were randomized by a computer-generated schedule to one of the two treatment groups (1:1) and were balanced within each site using a block size of 4. The sponsor staff, patients, and trial center personnel were blinded to trial treatment allocation.

The overall family-wise type I error rate for testing the primary and secondary efficacy end points was controlled at the 0.05 significance level using a 5-step serial gate-keeping multiple comparisons procedure; based on results of a previous phase 2b study (11), the sample size of 400 patients per treatment arm provided 85% power to simultaneously detect a difference between the placebo and linaclotide groups for all four primary efficacy end points.

Responder end points were analyzed using a Cochran-Mantel-Haenszel test controlling for geographic region. Continuous secondary end points and the IBS and constipation-severity end points were analyzed using an analysis of covariance model with fixed-effect terms for treatment group and geographic region and the corresponding baseline value as a covariate. The change-from-baseline means presented are the least-squares means (i.e., means adjusted for the other effects) from the analysis of covariance model based on patients' overall average scores (except for SBMs and CSBMs, for which overall weekly rates were calculated). Geographic region was used as a factor in the analyses as opposed to trial center due to the potential for trial centers to have small numbers of patients.

Patients were assumed not to have had BMs or to have taken rescue medications if the corresponding daily question was not answered. If a patient dropped out of the trial or otherwise did not report the efficacy data for a particular treatment-period week (patients were required to complete at least four interactive voice response system calls during a treatment week), then the patient was not considered as a responder for that week. An observed-cases approach to missing data was applied to the change-from-baseline secondary end points, such that if a patient dropped out of the study or otherwise did not report data, the average of the non-missing data over the 12 weeks (or 26 weeks) of the treatment period was the patient's value. All *P* values were based on two-sided tests.

All randomized patients who took at least one dose of study drug were included in safety analyses (safety population). Efficacy analyses were based on an intent-to-treat population, which included all patients in the safety population who had at least one post-randomization efficacy assessment (note: there was only one randomized patient who was not included in this intent-to-treat population).

RESULTS

Patient disposition, demographics, and baseline characteristics

Of the 2,340 patients who signed a consent form, 805 patients were randomized and received at least one dose of trial medication (safety population) (**Figure 1**). One patient was randomized and treated but did not have at least one post-randomization entry of the primary efficacy assessment. Thus, 804 patients were included in the intent-to-treat population. A total of 655 patients (81.5%) completed the first 12 weeks of the treatment period and 599 patients (74.4%) completed the entire 26-week treatment period. The treatment groups were well balanced with respect to demographics and baseline bowel and abdominal symptoms with the exception that the placebo group had a greater percentage of men than did the linaclotide group (12.7 vs. 8.2%, $P = 0.0379$) (**Table 1**). During the baseline period, 87% of patients experienced abdominal pain every day and 76% of patients had no CSBMs. Mean compliance with study-drug dosing (assessed by counting pills returned at study visits) up to study discontinuation/completion during the 26-week treatment period was 97.2 and 96.8% for the placebo and linaclotide groups, respectively.

Efficacy results

For all predefined primary and secondary efficacy end points, the linaclotide 290 µg group demonstrated statistically significant improvements compared with the placebo group, controlling for multiplicity.

A total of 33.7% of patients receiving linaclotide 290 µg compared with 13.9% of patients receiving placebo ($P < 0.0001$) met the combined responder requirements of the FDA end point over the first 12 weeks of the treatment period (odds ratio: 3.2, 95% confidence interval (CI): 2.2, 4.5) (**Figure 2**). Among linaclotide patients, 48.9% had ≥30% improvement in abdominal pain, and 47.6% had an increase in weekly CSBM rate of ≥1 for at least 6 of 12 treatment weeks, compared with 34.5 and 22.6% of

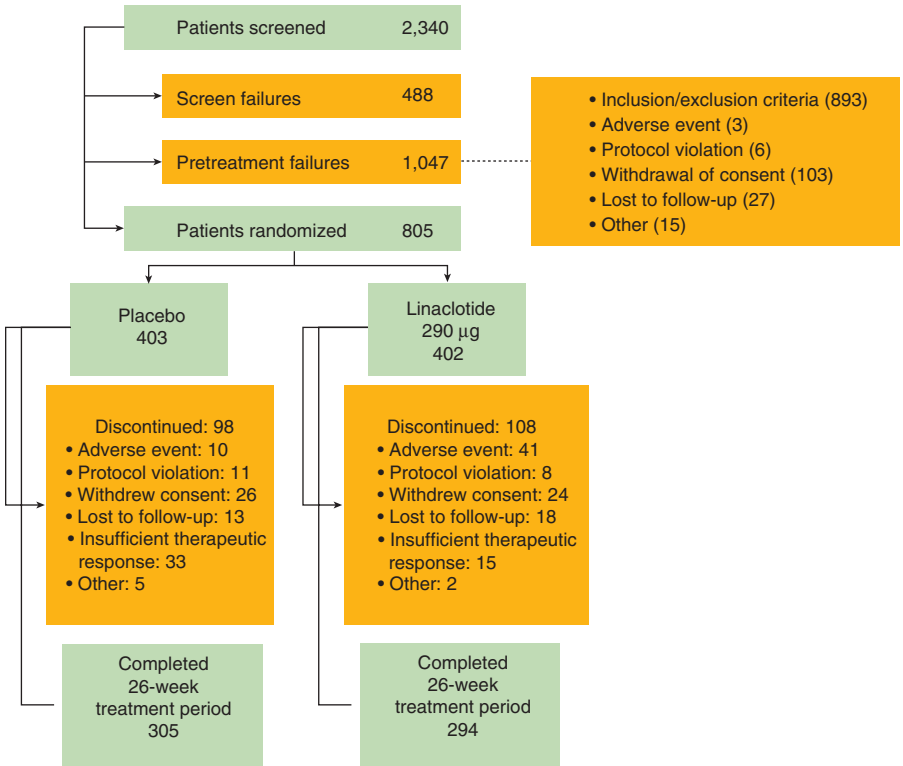

Figure 1. Patient flow through the trial.

placebo patients, respectively ($P<0.0001$, **Figure 2**). Similarly, 49.1 and 43.6% of linaclotide patients met these respective abdominal pain and CSBM components for at least 13 of 26 weeks, compared with 31.3 and 18.6% of placebo patients, respectively ($P<0.0001$, **Table 3**). Over the entire 26-week treatment period, 32.4% of patients receiving linaclotide and 13.2% of patients receiving placebo ($P<0.0001$) met the weekly responder requirements for the FDA end point for at least 13 out of the 26 weeks of the treatment period (odds ratio: 3.2, 95% CI: 2.2, 4.5). A greater percentage of linaclotide-treated than placebo-treated patients met the responder requirements for the other three primary end points, which required improvement for at least 9 of the first 12 weeks of the treatment period (**Table 2**). Numbers needed to treat for the primary end points ranged from 5.1 to 10.3 for the four primary end points.

Over the initial 12 weeks of the treatment period and the full 26-week treatment period, linaclotide-treated patients experienced statistically significantly greater improvements compared with placebo-treated patients for the change-from-baseline secondary end points and all additional end points (**Table 3**). Improvements from baseline for the symptoms of worst abdominal pain, abdominal bloating, abdominal fullness, and abdominal cramping were ~1 point higher on the 11-point numeric rating scale with linaclotide compared with placebo treatment over 12 and 26 weeks. The proportion of patients experiencing at least 30% improvement in bloating, cramping, and fullness for at least 50% of trial weeks ranged from 42 to 49% with linaclotide treatment vs. 23–35% with placebo treatment (**Table 2**).

For each week of the 26-week Treatment Period, the difference between linaclotide 290 µg and placebo was significant for percent change in worst abdominal pain ($P<0.001$, **Figure 3a**), change in worst abdominal pain ($P<0.0001$, **Figure 3b**), and change in SBM frequency ($P<0.0001$, **Figure 3c**). By week 26, linaclotide-treated patients had achieved 47% reduction in worst abdominal pain (vs. 25% for placebo-treated patients), and an average of 4.8 SBMs/week (vs. 2.5 for placebo-treated patients). Over 12 weeks, a statistically significantly greater percentage of linaclotide vs. placebo patients were responders for each level of percent improvement in worst abdominal pain (**Figure 3d**) and for each level of improvement in weekly SBMs (**Figure 3e**). Seventy-five percent of linaclotide-treated patients (vs. 61% of placebo-treated patients, $P<0.0001$) achieved minimal (at least 10%) improvement in worst abdominal pain, more than half (55 vs. 36% of placebo-treated patients, $P<0.0001$) achieved ≥30% improvement, and more than a third (34 vs. 14% of placebo-treated patients, $P<0.0001$) achieved ≥50% improvement. For SBMs, 88% of linaclotide-treated patients (vs. 69% of placebo-treated patients, $P<0.0001$) experienced an increase in weekly SBM frequency, 76% (vs. 46% of placebo-treated patients, $P<0.0001$) had an increase of ≥1 SBM/week, and 54% (vs. 15% of placebo-treated patients, $P<0.0001$) had an increase of ≥3 SBMs/week.

At the end of treatment, 45% of linaclotide-treated patients were either "very" or "quite" satisfied with treatment compared with 20% of placebo-treated patients ($P<0.0001$). In addition, a greater proportion of patients on linaclotide reported adequate relief compared with placebo following the treatment period, 56% compared with 33% ($P<0.0001$); for degree of relief of IBS symptoms, 72% of linaclotide-treated patients reported being "some what," "considerably," or "completely" relieved compared with 45% of placebo patients ($P<0.0001$).

Table 1. Summary of patient demographic and baseline characteristics (ITT population)

	Placebo (*N*=403)	Linaclotide 290 µg (*N*=401)
Demographic data		
Age (years), mean (range)	44.0 (18–87)	44.6 (19–82)
≥65 years, *n* (%)	17 (4.2)	23 (5.7)
Sex, *n* (%)		
Female	352 (87.3)	368 (91.8)
Male	51 (12.7)	33 (8.2)
Race, *n* (%)		
White	311 (77.2)	316 (78.8)
Black	78 (19.4)	70 (17.5)
Other	14 (3.5)	15 (3.7)
BMI, mean (s.d.)	27.7 (6.2)	27.8 (5.9)
Baseline data, mean (s.d.)		
Abdominal pain[a]	5.5 (1.7)	5.6 (1.7)
Abdominal discomfort[a]	6.0 (1.7)	6.1 (1.7)
Abdominal bloating[a]	6.5 (1.8)	6.6 (1.9)
Abdominal fullness[a]	6.5 (1.8)	6.7 (1.8)
Abdominal cramping[a]	5.2 (2.0)	5.4 (1.9)
CSBMs/week	0.2 (0.4)	0.2 (0.4)
SBMs/week	1.7 (1.4)	1.7 (1.4)
Stool consistency[b]	2.3 (1.0)	2.4 (1.1)
Straining[c]	3.5 (0.8)	3.6 (0.8)
Constipation severity[d]	3.8 (0.7)	3.8 (0.7)
IBS symptom severity[d]	3.7 (0.7)	3.7 (0.6)

BMI, body mass index; BSFS, Bristol Stool Form Scale; CSBM, complete SBM; SBM, spontaneous bowel movement; IBS, irritable bowel syndrome; ITT, intent-to-treat; NRS, numeric rating scale.

[a]Assessed using an 11-point NRS: 0=none; 10=severe.

[b]Assessed using the BSFS: 1=separate hard lumps, like nuts (hard to pass); 2=sausage-shaped, but lumpy; 3=like a sausage but with cracks on its surface; 4=like a sausage or snake, smooth and soft; 5=soft blobs with clear cut edges (passed easily); 6=fluffy pieces with ragged edges, a mushy stool; 7=watery, no solid pieces (entirely liquid).

[c]Assessed using a 5-point ordinal scale: 1=not at all, 2=a little bit, 3=a moderate amount, 4=a great deal, 5=an extreme amount.

[d]Assessed using a 5-point ordinal scale: 1=none; 2=mild; 3=moderate; 4=severe; 5=very severe.

All demographic and clinical characteristics were similar between treatment groups with the exception of sex (P=0.038).

Safety

A total of 263 patients (65.4%) in the linaclotide group and 228 patients (56.6%) in the placebo group experienced at

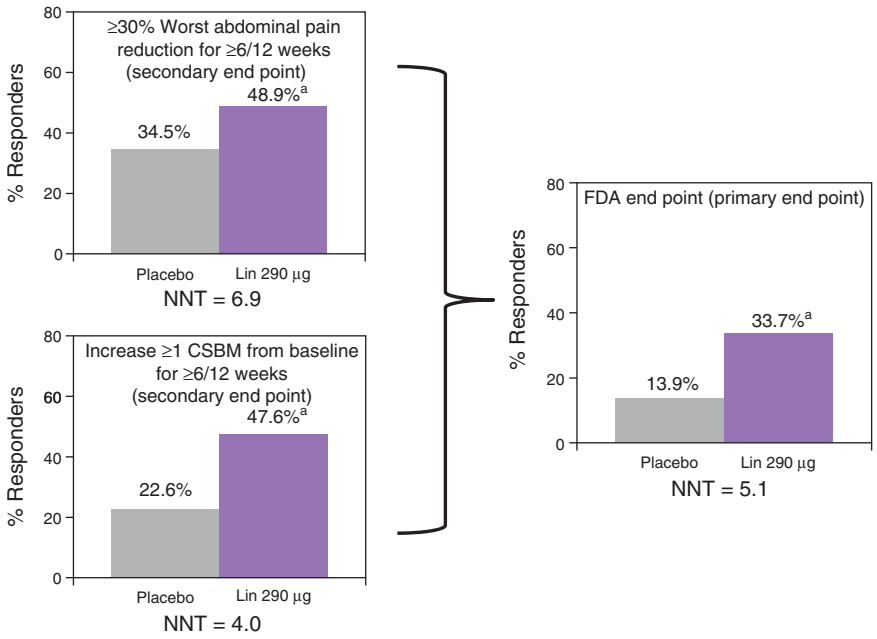

Figure 2. Food and Drug Administration (FDA) end point and components. FDA end point: ≥30% abdominal pain reduction and increase ≥1 complete spontaneous bowel movement (CSBM) from baseline in the same week for ≥6/12 weeks. *P* values were obtained from the Cochran-Mantel-Haenszel tests; all *P* values were <0.0001 and met the criterion for statistical significance based on the multiple comparisons procedure. Placebo, *N*=403; linaclotide 290 µg, *N*=401. NNT, number needed to treat. [a]*P*<0.0001 for all analyses based on a comparison of linaclotide vs. placebo groups using the Cochran-Mantel-Haenszel test.

Table 2. Efficacy parameter results, weeks 1–12 (primary end points) and weeks 1–26, ITT population

	Weeks 1–12			Weeks 1–26		
	Placebo (*N*=403) %	Linaclotide 290 µg (*N*=401) %	NNT (95% CI)	Placebo (*N*=403) %	Linaclotide 290 µg (*N*=401) %	NNT (95% CI)
FDA end point (at least 50% of weeks (i.e., 6/12 or 13/26 weeks))[a]	13.9	33.7	5.1 (3.9, 7.1)	13.2	32.4	5.2 (4.0, 7.3)
≥30% Decrease in average daily worst abdominal pain (at least 75% of weeks (i.e., 9/12 or 20/26 weeks))[a]	19.6	38.9	5.2 (3.9, 7.6)	17.4	36.9	5.1 (3.9, 7.4)
≥3 CSBMs and an increase of ≥1 CSBM from baseline (at least 75% of weeks (i.e., 9/12 or 20/26 weeks))[a]	5.0	18.0	7.7 (5.8, 11.5)	3.5	15.7	8.2 (6.2, 12.1)
Combined responder (decrease of ≥30% in the average daily worst abdominal pain score, ≥3 CSBMs, and an increase of ≥1 CSBM from baseline in the same week for at least 75% of weeks (i.e., 9/12 or 20/26 weeks))[a]	3.0	12.7	10.3 (7.5, 16.4)	2.5	12.0	10.5 (7.7, 16.8)

CI, confidence interval; CSBM, complete spontaneous bowel movement; FDA, Food and Drug Administration; ITT, intent-to-treat; NNT, number needed to treat.
[a]*P*<0.0001 for all analyses (*P* values were based on a comparison of linaclotide vs. the placebo group using the Cochran-Mantel-Haenszel test).

least one treatment-emergent AE (TEAE) during the 26-week treatment period ($P < 0.05$, **Table 4**). Most TEAEs were mild or moderate in severity; 7.7% of linaclotide patients and 4.7% of placebo patients had TEAEs rated as severe. SAEs were reported by four patients (1.0%) and seven patients (1.7%) in the linaclotide and placebo groups, respectively. The four SAEs reported in the linaclotide-treated patients were rotator cuff syndrome, appendicitis, cystopexy, and Hodgkin's disease. None of these SAEs was deemed by the site investigator to be related to linaclotide. A greater proportion of patients discontinued the study drug due to a TEAE in the linaclotide group compared with the placebo group (41 patients (10.2%) and 10 patients (2.5%), respectively). There were no deaths reported in this trial.

Table 3. Other efficacy parameter results (ITT population)

	Weeks 1–12			Weeks 1–26		
	Placebo (*N*=403)	Linaclotide 290 µg (*N*=401)	NNT (95% CI)	Placebo (*N*=403)	Linaclotide 290 µg (*N*=401)	NNT (95% CI)
Worst abdominal pain						
Mean (11-point NRS scale)	4.4	3.7		4.2	3.5	
[a]Change from baseline, mean[b,c]	−1.1	−1.9		−1.2	−2.1	
[a]% of patients with ≥30% decrease in worst abdominal pain for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	34.5	48.9	7.0 (4.7, 13.1)	31.3	49.1	5.6 (4.1, 8.9)
Abdominal discomfort						
Mean (11-point NRS scale)	4.9	4.1		4.7	3.9	
[a]Change from baseline, mean[b,c]	−1.1	−1.9		−1.3	−2.2	
% of patients with ≥30% decrease in discomfort for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	30.8	47.6	5.9 (4.3, 9.8)	28.8	48.1	5.2 (3.9, 7.8)
Abdominal bloating						
Mean (11-point NRS scale)	5.4	4.7		5.3	4.4	
[a]Change from baseline, mean[b,c]	−1.0	−1.9		−1.2	−2.2	
% of patients with ≥30% decrease in bloating for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	23.8	42.9	5.2 (3.9, 7.9)	25.1	42.4	5.8 (4.2, 9.2)
Abdominal fullness						
Mean (11-point NRS scale)	5.4	4.6		5.3	4.4	
Change from baseline, mean[b,c]	−1.1	−2.0		−1.2	−2.3	
% of patients with ≥30% decrease in abdominal fullness for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	23.3	42.9	5.1 (3.9, 7.6)	24.8	45.1	4.9 (3.7, 7.2)
Abdominal cramping						
Mean (11-point NRS scale)	4.1	3.5		3.9	3.3	
Change from baseline, mean[b,c]	−1.1	−1.8		−1.2	−2.0	
% of patients with ≥30% decrease in abdominal cramping for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	34.7	49.4	6.8 (4.7, 12.7)	33.3	48.4	6.6 (4.6, 11.9)
CSBMs						
Mean CSBMs/week	0.9	2.4		0.9	2.4	
[a]Change from baseline, mean[b,c]	0.7	2.2		0.7	2.2	
CSBM ≤24 h first dose (%)[d]	8.4	28.9	4.9 (3.9, 6.5)			
[a]% of patients w/ CSBM rate increase ≥1/week for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	22.6	47.6	4.0 (3.2, 5.4)	18.6	43.6	4.0 (3.2, 5.3)
SBMs						
Mean SBMs/week	3.0	5.7		2.8	5.5	
[a]Change from baseline[b,c]	1.3	4.0		1.1	3.8	
SBM ≤24 h after first dose (%)[d]	40.4	65.6	4.0 (3.1, 5.4)			
% of patients w/ SBM rate increase ≥2/week from baseline for at least 50% of weeks (i.e., 6/12 or 13/26 weeks)[d]	27.8	55.4	3.6 (2.9, 4.8)	21.6	49.6	3.6 (2.9, 4.6)
Stool consistency						
Mean BSFS score (1–7)	3.0	4.3		3.0	4.3	
[a]Change from baseline, mean[b,c]	0.6	1.9		0.6	1.9	
Mean weekly % SBMs without hard or lumpy stools (BSFS ≥3), mean[e]	61.1%	80.3%		62.1%	81.0%	

Table continued on following page

Table 3. Continued

	Weeks 1–12			Weeks 1–26		
	Placebo (*N*=403)	Linaclotide 290 µg (*N*=401)	NNT (95% CI)	Placebo (*N*=403)	Linaclotide 290 µg (*N*=401)	NNT (95% CI)
Straining						
Mean straining score (1–5)	2.9	2.3		2.8	2.3	
[a]Change from baseline, mean[b,c]	−0.7	−1.2		−0.7	−1.3	
Mean weekly % of SBM without significant straining (i.e., score ≤3), mean[e]	70.6%	82.4%		71.6%	83.5%	
Constipation severity						
Mean constipation severity score (1–5)	3.2	2.6		3.2	2.6	
Change from baseline, mean[b,c]	−0.6	−1.2		−0.6	−1.2	
% of patients reporting improvement ≥1 for at least 50% of the weeks (i.e., 6/12 weeks or 13/26 weeks)[d]	39.5%	60.8%	4.7 (3.6, 6.8)	34.5%	55.1%	4.8 (3.7, 7.2)
IBS severity						
Mean IBS severity score (1–5)	3.1	2.8		3.1	2.7	
Change from baseline, mean[b,c]	−0.6	−0.9		−0.6	−1.0	
% of patients reporting improvement ≥1 for at least 50% of the weeks (i.e., 6/12 weeks or 13/26 weeks)[d]	35.7%	55.4%	5.1 (3.8, 7.8)	31.8%	53.1%	4.7 (3.6, 6.8)
Adequate relief						
% of patients reporting adequate relief of IBS symptoms for at least 75% of the weeks (i.e., 9/12 or 20/26 weeks)[d]	17.6	41.9	4.1 (3.3, 5.5)	14.6	35.7	4.8 (3.7, 6.6)
% of patients reporting adequate relief of IBS symptoms for at least 50% of the weeks (i.e., 6/12 or 13/26 weeks)[d]	25.6	54.6	3.4 (2.8, 4.4)	25.1	49.1	4.2 (3.3, 5.7)
Degree of relief[f]						
% of patients reporting "somewhat relieved," "considerably relieved," or "completely relieved" for 100% of the weekly scores or "considerably relieved" or "completely relieved" for at least 50% of the weekly scores[d]	21.1	45.4	4.1 (3.3, 5.6)	17.6	37.9	4.9 (3.8, 7.0)

ANOVA, analysis of variance; ANCOVA, analysis of covariance; BSFS, Bristol Stool Forms Scale; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSBM, complete SBM; IBS, irritable bowel syndrome; ITT, intent-to-treat; NRS, numerical rating scale; NNT, number needed to treat; SBM, spontaneous bowel movement.

[a]Secondary end point for weeks 1–12.

[b]Changes from baseline are the least-squares means from the ANCOVA model.

[c]*P* values were based on a comparison of linaclotide vs. the placebo group using the ANCOVA model. $P<0.0001$ for all analyses.

[d]*P* values were based on a comparison of linaclotide vs. the placebo group using the CMH test. $P<0.0001$ for all analyses.

[e]*P* values are based on a comparison of linaclotide vs. placebo using the ANOVA model. $P<0.0001$ for all analyses.

[f]Degree of relief scale: 1=completely relieved, 2=considerably relieved, 3=somewhat relieved, 4=unchanged, 5=somewhat worse, 6=considerably worse, 7=as bad as I can imagine.

Diarrhea was the most frequently reported TEAE among linaclotide-treated patients, reported by 79 patients (19.7%) in the linaclotide group compared with 10 patients (2.5%) in the placebo group ($P<0.0001$). In the placebo group, 2.2% of patients experienced mild diarrhea, 0.2% of patients experienced moderate diarrhea, and no patient experienced severe diarrhea; in the linaclotide group, 7.7% of patients experienced mild diarrhea, 10.0% experienced moderate diarrhea, and 2.0% experienced severe diarrhea. Of the 79 linaclotide-treated patients who developed diarrhea, 48.1% had onset within the first week and 75.9% had onset within the first 4 weeks of initiating therapy. Discontinuation of study drug due to diarrhea occurred in 18 patients (4.5%) in the linaclotide group compared with 1 patient (0.2%) in the placebo group. There were no SAEs of diarrhea reported during the trial. None of the patients who reported diarrhea experienced clinically significant sequelae (e.g., orthostatic hypotension or dehydration).

There were no clinically meaningful differences between the linaclotide and placebo groups in the incidence of abnormal laboratory parameters, vital signs, or ECG parameters. Serum bicarbonate levels were below the lower limit of normal at the end of treatment in five patients receiving linaclotide. One of these patients reported diarrhea as an AE. No bicarbonate levels below the lower limit of normal were reported in patients receiving placebo.

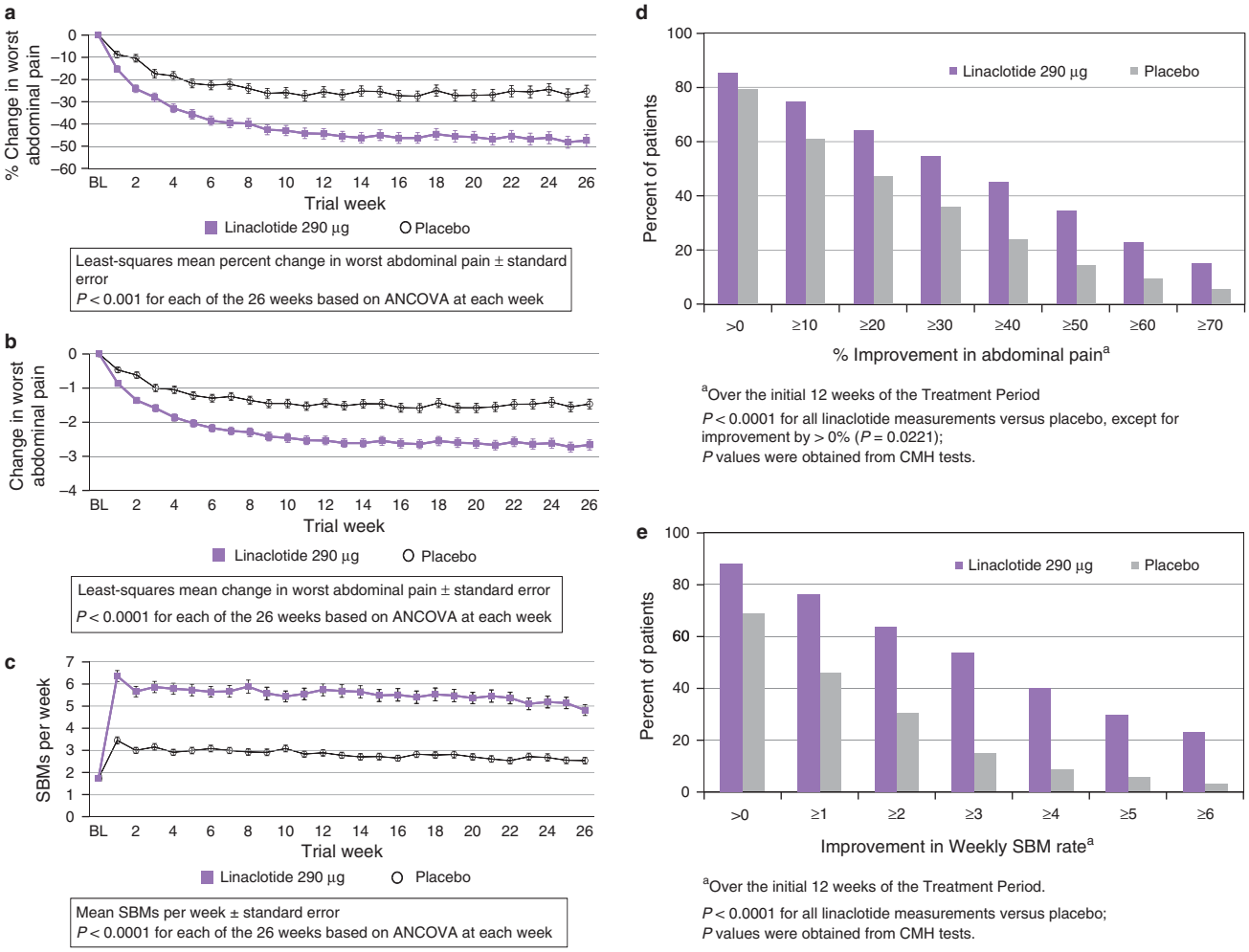

Figure 3. Changes in abdominal pain and SBM rate by week and by improvement level. (**a**) Twenty-six weekly results for percent change in worst abdominal pain. $P<0.0001$ for linaclotide 290 µg vs. placebo for all weeks except week 1 ($P=0.0007$); P values were obtained from an analysis of covariance (ANCOVA) model. (**b**) Twenty-six weekly results for change in worst abdominal pain. $P<0.0001$ for linaclotide 290 µg vs. placebo for all weeks; P values were obtained from an ANCOVA model. (**c**) Twenty-six weekly results for spontaneous bowel movement (SBM) frequency. $P<0.0001$ for linaclotide 290 µg vs. placebo for all weeks; P values were obtained from an ANCOVA model. (**d**) Incremental improvements in worst abdominal pain. All P values were <0.0001 for linaclotide 290 µg vs. placebo, except for >0% category ($P=0.0221$); P values were obtained from Cochran-Mantel-Haenszl (CMH) tests. (**e**) Incremental improvements in SBM frequency. All P values were <0.0001 for linaclotide 290 µg vs. placebo; P values were obtained from CMH tests.

In the subset of patients who were assessed for linaclotide exposure, 2 (2.0%) of the 98 linaclotide patients and none of the 93 placebo patients had levels of linaclotide just above the lower limit of quantification of 0.2 ng/ml following their initial dose (values: 0.241 and 0.239 ng/ml). None of the patients in either group had quantifiable plasma levels of linaclotide's primary metabolite, MM-419447 (<2.0 ng/ml) following the initial dose or at week 4.

DISCUSSION

In this phase 3 clinical trial in patients with IBS-C, linaclotide treatment resulted in significantly greater percentages of patients who experienced improvements in abdominal and bowel symptoms compared with placebo treatment. For the rigorous end point recommended for IBS-C in the recently finalized FDA guidance for IBS clinical trials (May 2012) (14), the percentage of responders was 33.7% in the linaclotide group compared with 13.9% in the placebo group ($P<0.0001$). Significant differences in favor of linaclotide ($P<0.0001$) were also observed for an even more rigorous end point that required for at least 9 out of the 12 weeks of the treatment period that patients meet the ≥30% of improvement in worst abdominal pain and both ≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline. The effects of linaclotide on abdominal and bowel symptoms were manifested within the first week of treatment and sustained over the entire 26-week treatment period.

Abdominal pain is the key clinical feature and, arguably, the most difficult symptom to treat in patients suffering from IBS (17). In this trial, linaclotide improved worst abdominal pain as demonstrated by a significant decrease in absolute worst abdominal pain score and a greater proportion of patients

Table 4. Treatment-emergent adverse events (safety population, 26 weeks)

Adverse event (preferred term)	Placebo (*N*=403) *n* (%)	Linaclotide 290 µg (*N*=402) *n* (%)
Patients with at least one TEAE	228 (56.6)	263 (65.4)[a]
Diarrhea	10 (2.5)	79 (19.7)[a]
Upper respiratory tract infection	22 (5.5)	22 (5.5)
Abdominal pain	16 (4.0)	18 (4.5)
Flatulence	9 (2.2)	15 (3.7)
Viral gastroenteritis	9 (2.2)	15 (3.7)
Headache	11 (2.7)	13 (3.2)
Abdominal distension	6 (1.5)	9 (2.2)
Gastroesophageal reflux disease	6 (1.5)	9 (2.2)

[a]The incidence of patients with at least one TEAE was significantly greater in the linaclotide group ($P<0.05$), based on a Fisher's exact test comparing the linaclotide dose and placebo. With the exception of diarrhea ($P<0.0001$), the incidence of adverse events (AEs) displayed was not significantly different between groups.

Treatment-emergent adverse events (TEAEs) reported in ≥2% of linaclotide-treated patients and at an incidence greater than reported in placebo-treated patients during the treatment period.

n=Number of patients with TEAEs, irrespective of relationship to study drug.

Patients were counted only once within each preferred term.

Adverse events reported in ≥2% of linaclotide patients and at a higher incidence than in placebo patients during the 26-week treatment period.

reporting ≥30% reduction in abdominal pain. A 30% reduction in pain score has been suggested as the threshold for a moderately clinically important within-group improvement, based on anchoring methods linking such improvements to patient reports of feeling "much better" or "much improved" (18–21). The improvement in worst abdominal pain over placebo was statistically significant starting from the first week of therapy and continuing through all subsequent weeks of therapy, such that the mean percent improvement in worst abdominal pain was ~50% by the end of the 26 weeks of treatment (**Figure 2a**).

In addition to abdominal pain, linaclotide treatment resulted in significant improvements in other key abdominal symptoms, including discomfort, fullness, cramping, and bloating. Like abdominal pain, improvements in these symptoms occurred within the first week of therapy, were maximal by the 12th week (the primary assessment period), and were subsequently sustained over the remainder of the 26-week treatment period. In aggregate, improvements in abdominal symptoms suggest an effect of linaclotide on visceral sensation, consistent with preclinical data demonstrating that linaclotide treatment can reduce visceral pain in models of hyperalgesia (9). Linaclotide's effects are believed to be a result of GC-C mediated elevation of extracellular cGMP, which has been shown to reduce the firing of afferent pain fibers in *ex-vivo* models of visceral nociception (10). It is conceivable that improvements in constipation may also contribute to the effects of linaclotide on abdominal symptoms. Further studies to more completely elucidate the mechanisms that underlie linaclotide's favorable effects on abdominal symptoms are under way.

Several issues must be considered when interpreting the results of this clinical trial. The Rome II (22), rather than Rome III (1), diagnostic criteria were used in this trial for several reasons. The Rome III criteria were relatively new, with limited use in clinical trials, at the time that this trial was being designed. In addition, earlier phase 2 IBS-C studies with linaclotide (11,12) used the Rome II criteria and, therefore, the Rome II criteria were selected to maintain consistency throughout the linaclotide development program. Nevertheless, in this study, all but one randomized patient meeting the Rome II criteria for IBS also met the Rome III criteria.

The FDA's primary end point was intended to establish a threshold response at an individual-patient level across the two hallmark symptoms in IBS-C, abdominal pain, and constipation (assessed as CSBM frequency). However, when continuous data are dichotomized into responder and non-responder categories, much information about the patient's response to a treatment is lost (23). Requiring that a patient simultaneously meet multiple thresholds in a combined responder definition, although relevant if those thresholds are clinically meaningful, may be overly restrictive when partial responses or responses to less rigorous but still clinically meaningful responder criteria are ignored. To more fully understand the potential benefit of a new therapy for IBS-C and its differentiation from an active or placebo control, it is important to evaluate the distribution of abdominal pain and CSBM efficacy across a full range of responses.

The most common TEAE was diarrhea. The observation that diarrhea occurred more commonly with linaclotide than with placebo was not surprising, as diarrhea represents an extension of linaclotide's pharmacology. Ninety percent of the reported diarrhea events were mild or moderate in severity and only 4.5% of linaclotide-treated patients discontinued treatment due to diarrhea. Twenty-eight percent of patients reporting diarrhea experienced this AE on the first day of therapy and seventy-six percent within the first 4 weeks of treatment.

In conclusion, in this large, methodologically rigorous, 26-week phase 3 trial in patients with IBS-C, linaclotide improved worst abdominal pain and other abdominal and bowel symptoms associated with IBS-C, while decreasing constipation and IBS severity. AEs were generally comparable between linaclotide and placebo groups, with the exception of diarrhea, which occurred more commonly with linaclotide than with placebo, and was mostly mild or moderate in severity. Therefore, linaclotide has the potential to offer relief for the multiple symptoms from which patients with IBS-C suffer.

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Annie Neild, PhD, of Ironwood Pharmaceuticals, provided editorial assistance. Portions of this manuscript were presented as an oral presentation at Digestive Disease Week, May 2011, Chicago, IL.

CONFLICT OF INTEREST

Guarantor of the article: Jeffrey M. Johnston, MD.

Specific author contributions: Wrote the initial draft of the manuscript and assisted in the interpretation of data: William D. Chey and Anthony Lembo; designed the trial: Jeffrey Johnston and Bernard Lavins; assisted in the interpretation of data and critical revision of the manuscript for important intellectual content: Jeffrey Johnston, Bernard Lavins, Caroline Kurtz, Mark Currie, Harvey Schneier, and Steven Shiff; provided statistical design, plan, analyses, and interpretation: James MacDougall, Xinwei Jia, and James Shao; coordinated acquisition of data and trial supervision: Donald Fitch and Mollie Baird.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The key features of irritable bowel syndrome with constipation (IBS-C) are abdominal pain and constipation-related complaints including hard stools, straining, and a sense of incomplete evacuation.
- ✓ Few medical therapies have proven effective for the multiple symptoms of IBS-C.
- ✓ Linaclotide is a minimally absorbed 14-amino-acid peptide guanylate cyclase-C agonist.
- ✓ In phase 2 clinical studies, linaclotide accelerated colonic transit and improved abdominal pain and constipation associated with IBS-C.

WHAT IS NEW HERE

- ✓ In this phase 3 trial, linaclotide-treated patients vs. placebo-treated patients experienced statistically significant and sustained improvements in abdominal pain and stool frequency over the 26-week treatment period.
- ✓ Linaclotide improved other important irritable bowel syndrome with constipation (IBS-C) symptoms including bloating, stool consistency, and straining.
- ✓ Linaclotide led to a significantly greater proportion of patients reporting adequate relief of their IBS-C symptoms than placebo.
- ✓ The most common adverse event with linaclotide treatment was diarrhea.

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